The 36th Annual
Southeastern Consortium For CME in Dermatology

Patient Presentations / Clinical Session

Sunday, October 28, 2012

Patient Presentations
Ambulatory Care Center (ACC)
100 Mason Farm Road
Chapel Hill, NC 27599

Clinical Session
Medical Biomolecular Research Bldg. (MBRB)
103 Mason Farm Road
Chapel Hill, NC 27599

UNC SCHOOL OF MEDICINE

Patient Presentations

Ambulatory Care Center (ACC)
UNC Campus
100 Mason Farm Road
Chapel Hill, NC 27599

7:20 am	Shuttle departs Courtyard Marriott
7:45 am	Registration/Continental Breakfast – 2nd floor lobby
8:30 am	Patient Viewing – 3rd floor

Clinical Session

Medical Biomolecular Research Building (MBRB)
UNC Campus
103 Mason Farm Road
Chapel Hill, NC 27599

Moderators:
Craig Burkhart, MD
Dean Morrell, MD

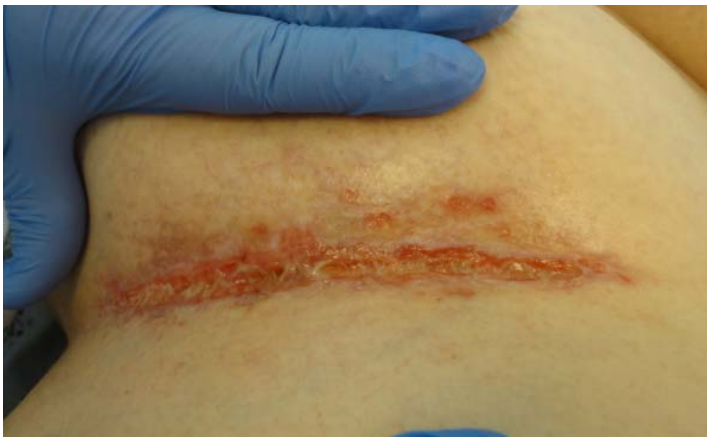
10:15 am	Case Discussions – Room G202
12:00 pm	Adjournment
12:20 pm	Shuttle departs for Courtyard Marriott (from the ACC Building)

Table of Contents

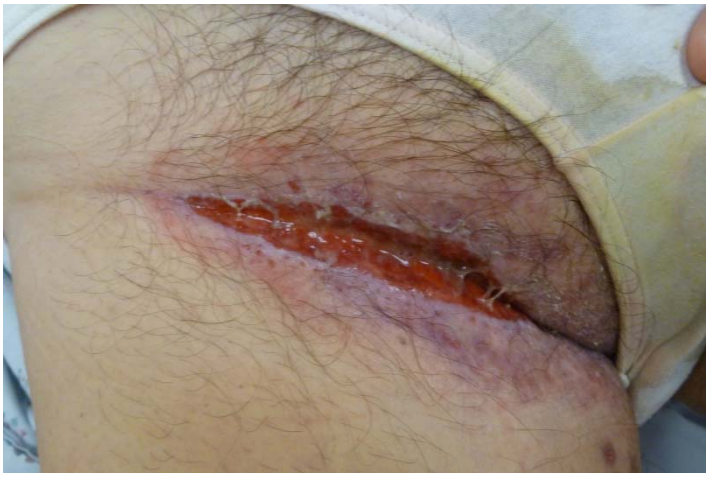
Table of Contents

Case 1: Cutaneous Crohn's Disease

- Clinical Presentation: Classically, knife wound-like ulcerations are seen in the inguinal folds, crura, inframammary folds, and below the pannus. Violaceous plaques, nodules, and ulcers can also be seen in any location. In children, violaceous induration in the genital and perianal areas is common.

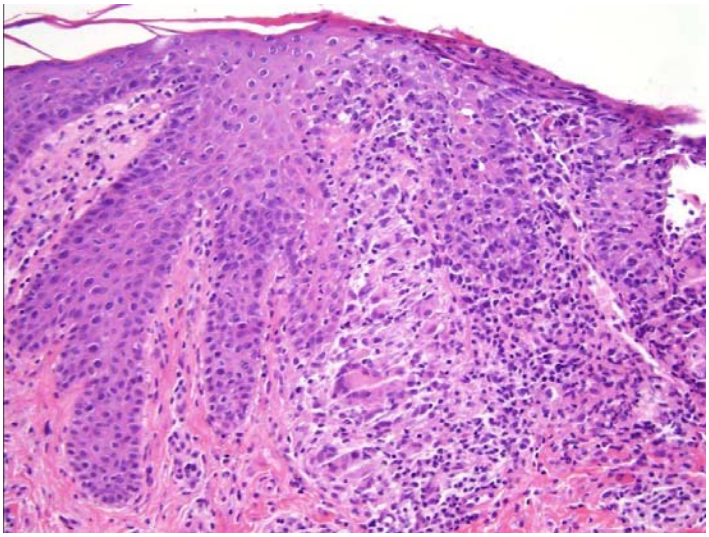


- Pathophysiology: Th1- and Th17-mediated granulomatous cutaneous inflammation associated with underlying Crohn's disease.



- Pathology: Dense, nodular, non-caseating granulomatous inflammation, commonly with multinucleated giant cells, neutrophils, and lymphocytes.

- Evaluation/Management: Non-caseating granulomatous dermatitis on pathology should trigger a thorough review of systems and colonoscopy when indicated. Screening for tuberculosis and tissue cultures are necessary to rule out infection. Sarcoidosis must also be considered in the appropriate clinical context. Treatment is similar to therapy for the underlying bowel disease, but cutaneous disease may continue despite stabilization of GI disease.



- Up to 20% of adults and 80% of children present without history of inflammatory bowel disease. Children more often present with genital swelling and discoloration, which can prompt concern for child abuse.

Case 2: Palisaded and Neutrophilic Granulomatous Dermatitis

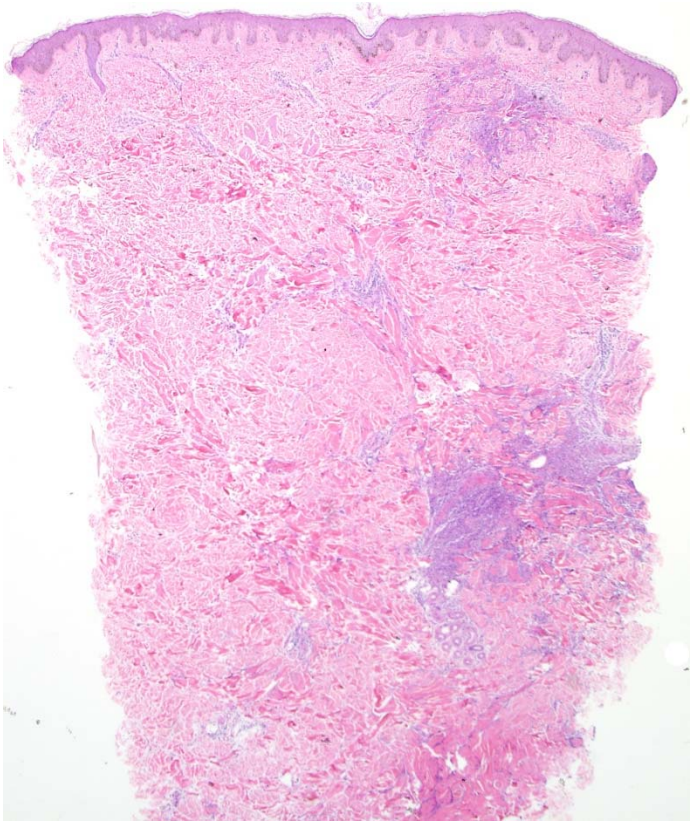
- Clinical Presentation: Most commonly, 2-20mm infiltrated papules favoring extensor surfaces in the setting of autoimmune arthritis or connective tissue disease, but annular and linear plaques are also reported. It can affect any area, in this case primarily the trunk.

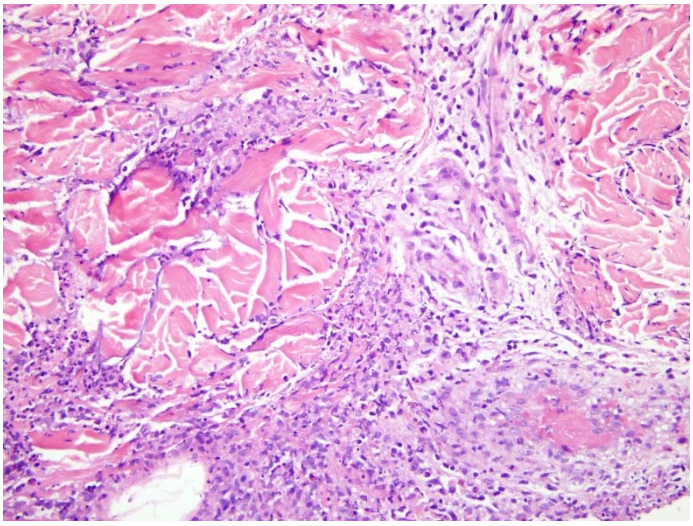
- Pathophysiology: Thought to be an immune complex-mediated small vessel vasculitis as a result of underlying autoimmune disease.

- Pathology: Palisaded histiocytes with surrounding neutrophilic infiltrate and thickened, basophilic collagen. This can extend to the subcutis, and small vessel vasculitis is often prominent.

- Evaluation/Management: Workup for underlying connective tissue disease or other autoimmune syndromes is mandatory. Management parallels the underlying autoimmune condition; dapsone and other immunomodulators have been helpful in some cases.

- Interstitial granulomatous dermatitis with arthritis is thought to be a related condition. It also presents in the background of autoimmune disease, but lacks vasculitis on pathology and favors the trunk of females.





Case 3: Epidermolysis Bullosa Acquisita

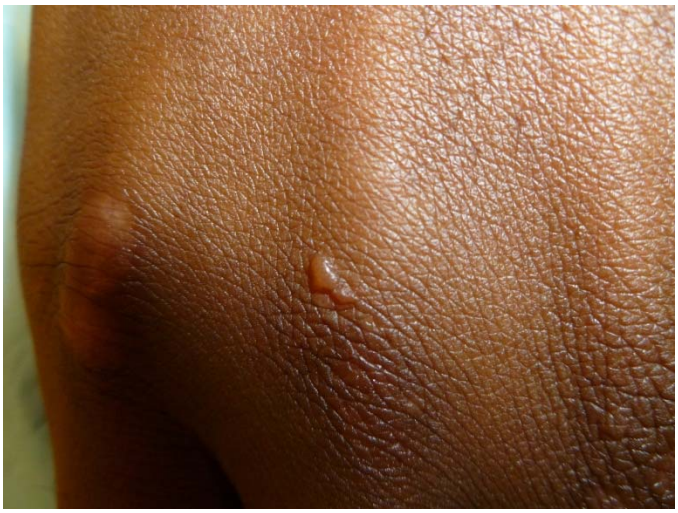
- Clinical Presentation: Typically presents with non-inflammatory mechanically-induced bullae on acral and extensor surfaces with milia, pigment alteration, and scarring similar to dystrophic epidermolysis bullosa. Severe cases may be mutilating. An inflammatory bullous pemphigoid-like presentation can occur. Ocular, oral, and scalp involvement is not infrequent. Pediatric cases have been reported.

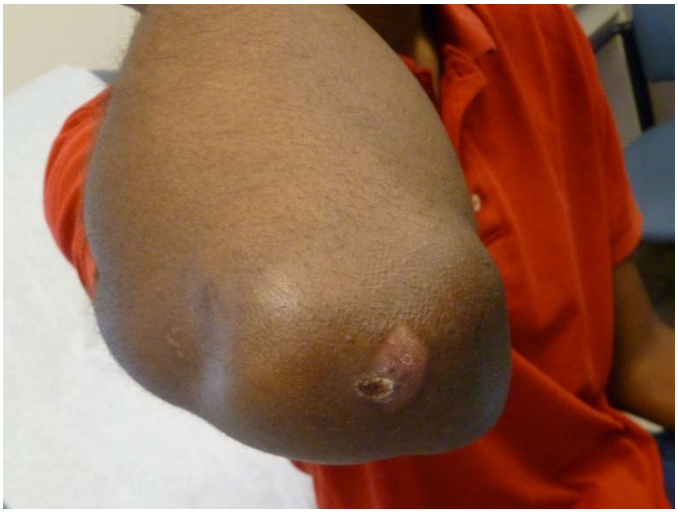
- Pathophysiology: IgG to type VII collagen, most commonly in the NC1 domain, disrupts anchoring fibrils and causes a subepidermal split.

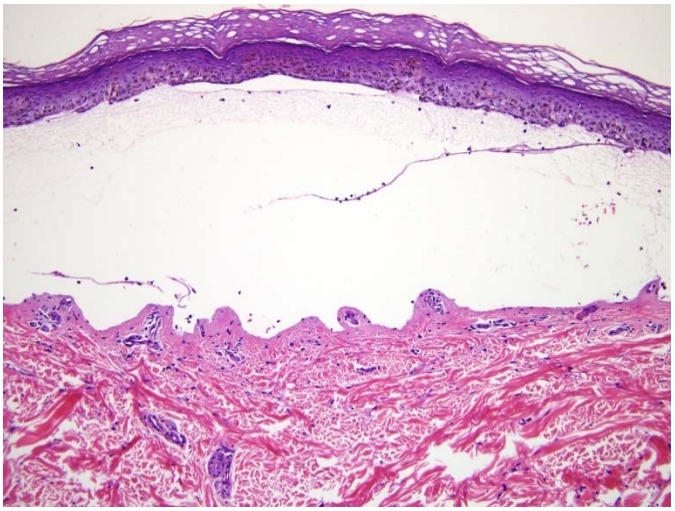
- Pathology: Inflammation is minimal or absent in the mechanobullous subtype and fulminant with eosinophils, lymphocytes, and neutrophils in the inflammatory subtype. DIF shows linear IgG with occasional C3, IgM, or IgA at the BMZ. IIF shows IgG on the floor of salt-split skin in 50%. EM, western blot, and ELISA can be helpful.

- Evaluation/Management: Histology and IF studies can distinguish it from other autoimmune and inherited blistering disorders. Immunomodulating therapies are variably effective. Crohn's disease may be associated in some patients.

- This patient presented with the mechanobullous disease with a pauci-inflammatory subepidermal split, linear IgG on DIF, and negative IIF.







Case 4: Hermansky-Pudlak Syndrome

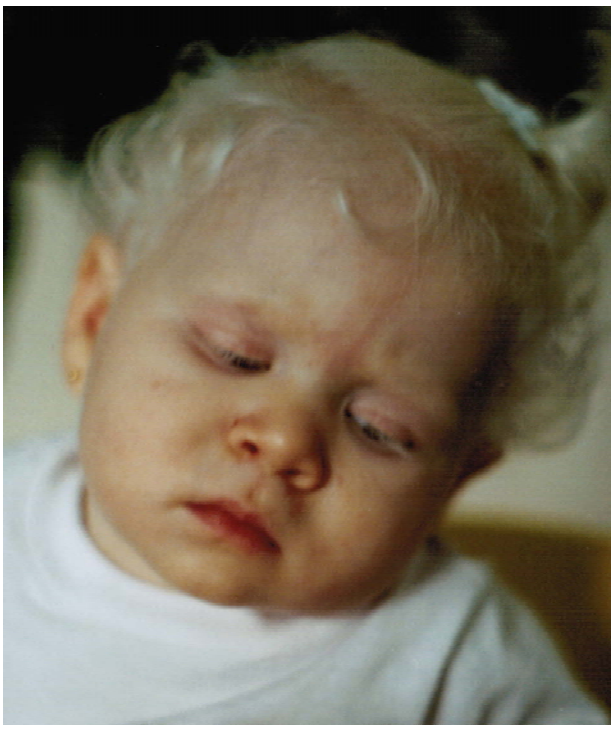
- Clinical Presentation: Variable pigment dilution, nystagmus, poor vision, photophobia, and platelet dysfunction with prolonged bleeding are the initial signs. Pulmonary fibrosis and granulomatous colitis present in the 3rd and 4th decades and result in mean life expectancy of 37 years. Type 2 may present with immunodeficiency as well.

- Pathophysiology: Autosomal recessive defects in protein trafficking for forming melanosomes and other lysosome-related organelles, i.e. BLOC proteins and AP3. This leads to aberrant melanosome development, accumulation of ceroid proteins in macrophages, and platelet dysfunction.

- Evaluation: Genetic sequencing or tyrosinase assays rule out oculocutaneous albinism. Absent platelet dense granules are seen on EM. Granulomatous colitis and pneumonitis with ceroid deposition can be detected. PFTs are performed to follow pulmonary fibrosis. Monitor patients for renal impairment and cardiomyopathy.

- Management: Sun protection, platelet transfusions prior to procedures, referral to pulmonology and gastroenterology. Lung transplant has been life-prolonging in some patients.

- 1/1,800 in Puerto Rico are affected. Eight subtypes exist.



Case 5: Porokeratosis Palmaris, Plantaris, et Disseminata

- Clinical Presentation: Hyperkeratosis of the palms and soles followed by hyperkeratotic, classically annular or punctate papules on the trunk and extremities with onset in adulthood.

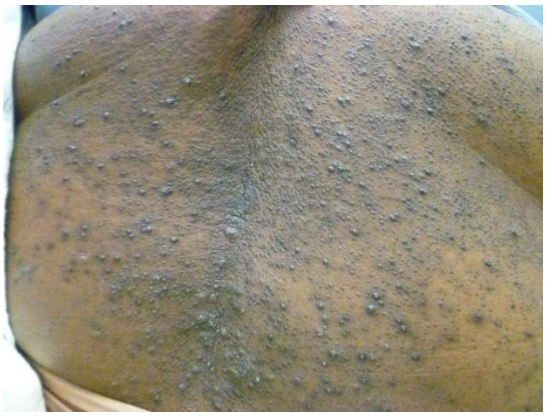
- Pathophysiology: PPPD is thought to be an abnormal reaction of epidermal cells to immunological or environmental triggers. There are cases of autosomal dominant inheritance, but others are sporadic. The causative gene or genes have not been identified.

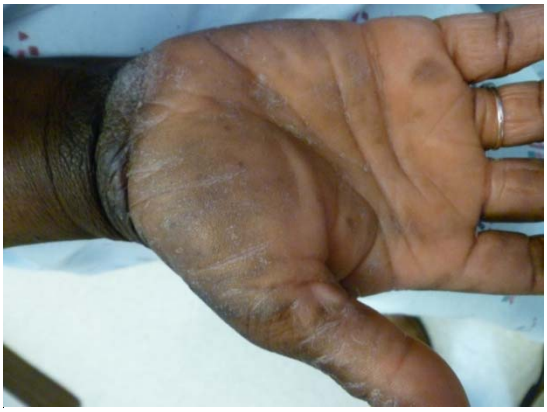
- Pathology: Identical to other forms of porokeratosis: porokeratosis with foci of cornoid lamellation, consisting of tiers of parakeratosis above dyskeratotic keratinocytes with focal granular layer loss.

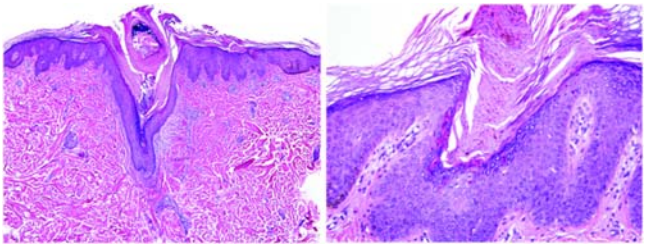
- Evaluation: Though case reports of squamous cell carcinoma arising within lesions of PPPD are rare, these patients should be regularly monitored for suspicious lesions.

- Management: Topical and systemic retinoids as well as keratolytics have been tried with very limited success.

- No other reports of scalp involvement and alopecia have been made; only one other reported case was in an African-American patient.







Case 6: Ulcerative Cutaneous Lupus Erythematosus

- Clinical Presentation: Ulcerative lesions occurring on the feet and groin in a patient with clinical, laboratory and pathological diagnosis of cutaneous lupus erythematosus. She had a positive ANA at >1:640 with a speckled pattern and highly positive α-RNP.

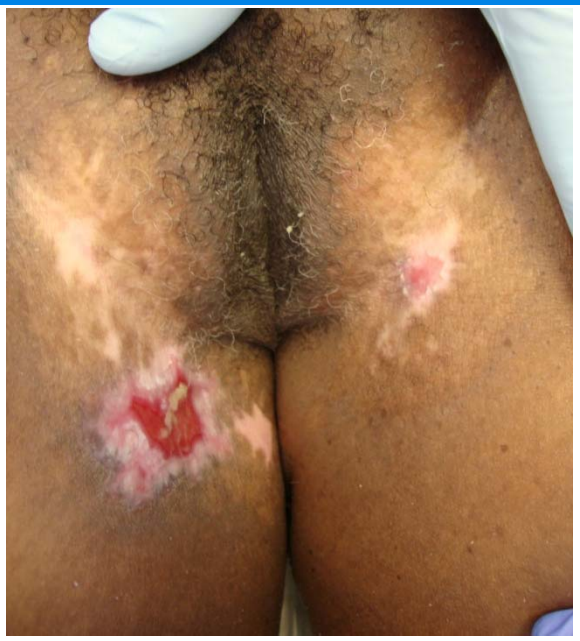
- Pathophysiology: Unclear; likely part of the spectrum of autoimmune reactivity of lupus erythematosus and other connective tissue diseases.

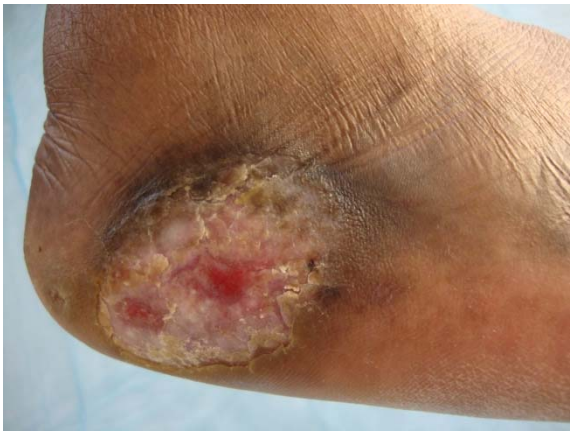
- Pathology: Superficial and deep perivascular and focal periadnexal inflammatory infiltrate with overlying interface dermatitis consisting of lymphocytes at the DEJ with degenerative changes and subepidermal clefting. There is hypergranulosis and orthokeratosis.

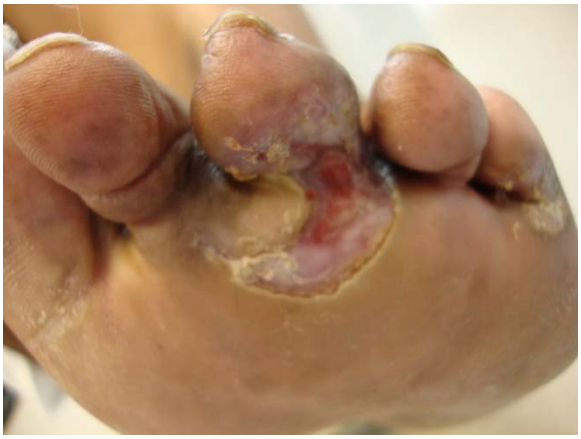
- Evaluation: Biopsy, laboratory panel including autoantibodies (ANA, ENA, α-dsDNA) as well as C3, C4, CBC, BUN, and creatinine.

- Management: Oral hydroxychloroquine, topical steroids, wound care; other immunosuppressive medications may be required.

- There is a well-described phenomenon of lichen planus coexisting or overlapping with lupus erythematosus. Pathology, at times, can be similar. Response to treatment in these patients is often poor.







Case 7: Erythropoietic Protoporphyria

- Clinical Presentation: Immediate cutaneous photosensitivity with pain, erythema, edema, and blistering beginning in childhood with subsequent mild waxy scarring.

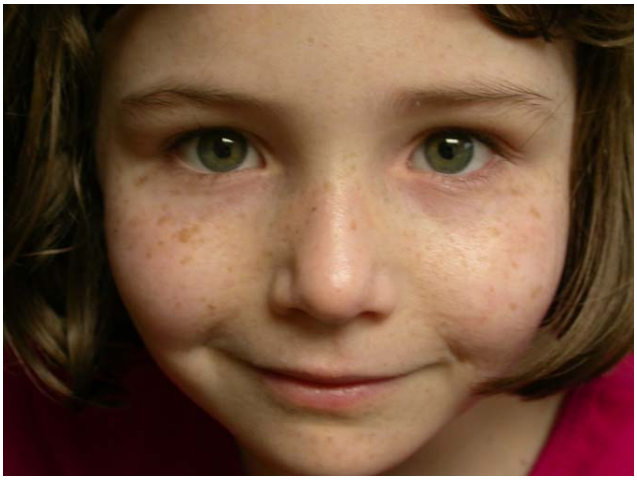
- Pathophysiology: Autosomal dominant deficiency of ferrochelatase (last enzyme in the heme biosynthetic pathway).

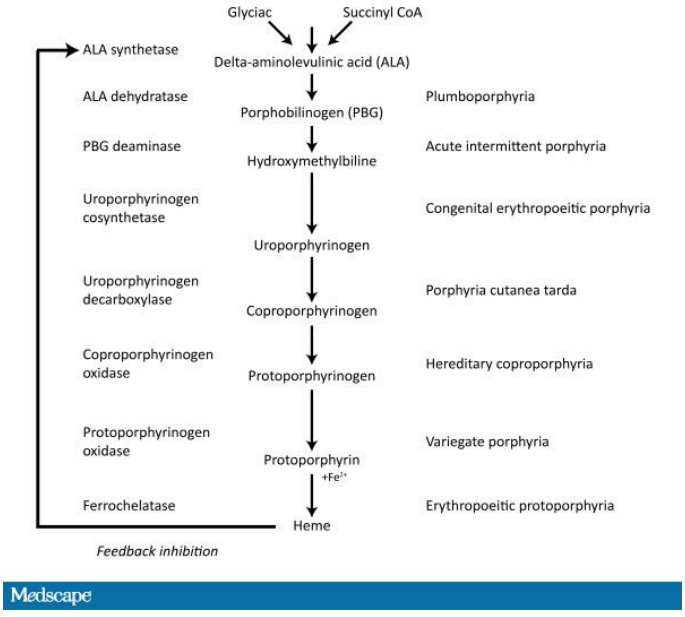
- Pathology: Vacuolization of epidermal cells in acute lesions; eosinophilic PAS-positive deposits around blood vessels in chronic lesions.

- Evaluation: Free erythrocyte protoporphyrin test positive (protoporphyrin is elevated in erythrocytes and plasma). Urine porphyrins are negative. Copro- and protoporphyrins are elevated in feces. LFTs and bilirubin should be monitored at least yearly and CBC monitored for anemia.

- Management: Rigorous sun protection and beta-carotene dosed by age.

- The second most common cutaneous porphyria. Up to 5% of patients can develop severe liver disease. Gallstones are common.





Case 8: Viral-Associated Trichodysplasia

- Clinical Presentation: Follicularly-based spiny papules and alopecia in immunosuppressed individuals, predominantly on the central face.

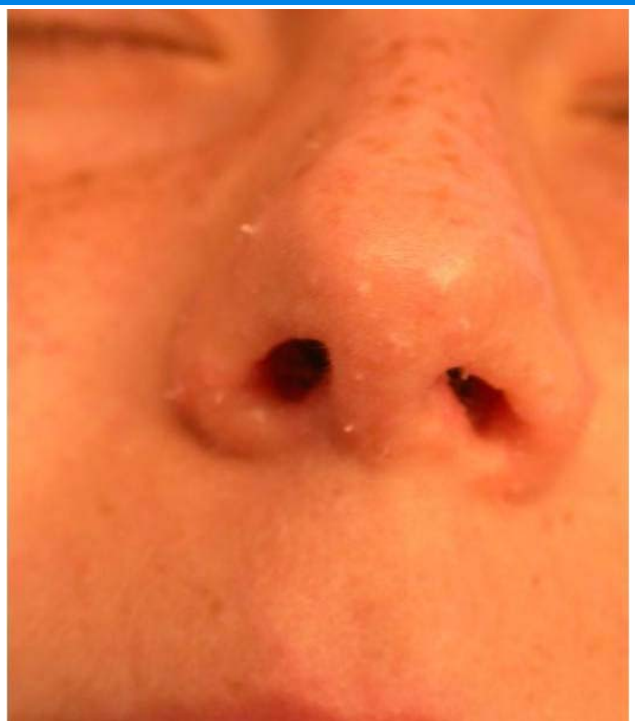
- Pathophysiology: Folliculocentric activation of the human polyomavirus trichodysplasia spinulosa-associated virus (TSV). However, 4% of unaffected immunosuppressed patients were found to harbor this virus, so the pathophysiology may be more complex.

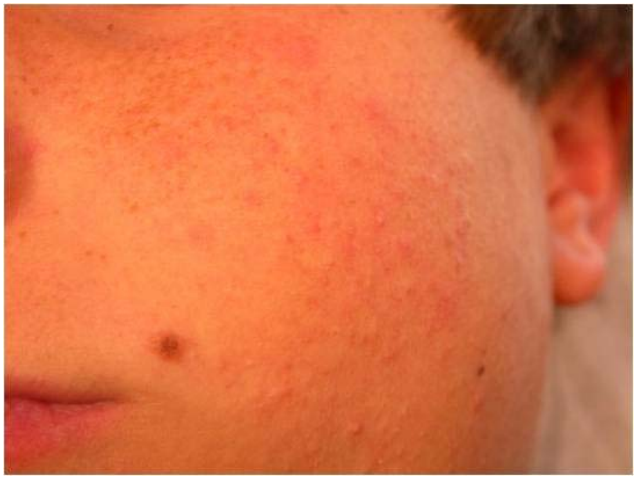
- Pathology: Aberrant keratinization of the inner root sheath hair shaft cells with enlarged, bulbous anagen hairs and enlarged bluish gray inclusions within germinative cells transitioning to inner root sheath–type cells; vacuolated keratinocytes with pyknotic nuclei and coarse keratohyaline granules are seen.

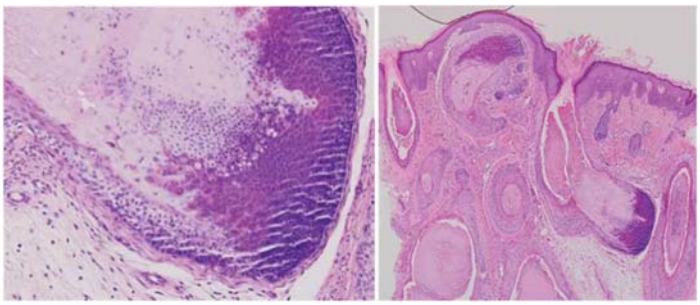
- Evaluation: Diagnosis can be confirmed, if needed, with immunohistochemistry (staining for polyomavirus middle T antigen) and PCR (for TSV).

- Management: There has been some treatment success with topical cidofovir or, if needed, systemic valganciclovir.

- Occurs most typically in patients receiving immunosuppression after solid organ transplant (classically, being treated with cyclosporine) or with acute lymphocytic leukemia.







Case 9: Pachyonychia Congenita

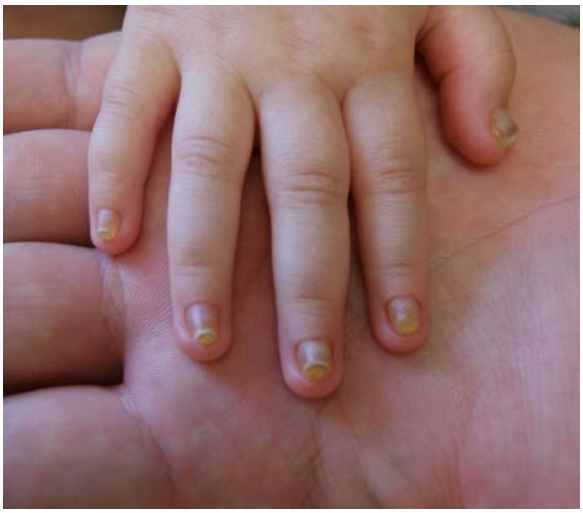
- Clinical Presentation: Variable expression of focal PPK, “doorstop” nails, pilosebaceous cysts (steatocystoma, vellus hair cysts), follicular hyperkeratosis, oral leukokeratosis (not pre-malignant), and natal teeth. The diagnostic triad of toenail thickening, plantar keratoderma, and plantar pain was reported by 97% of patients with PC by age 10 years.

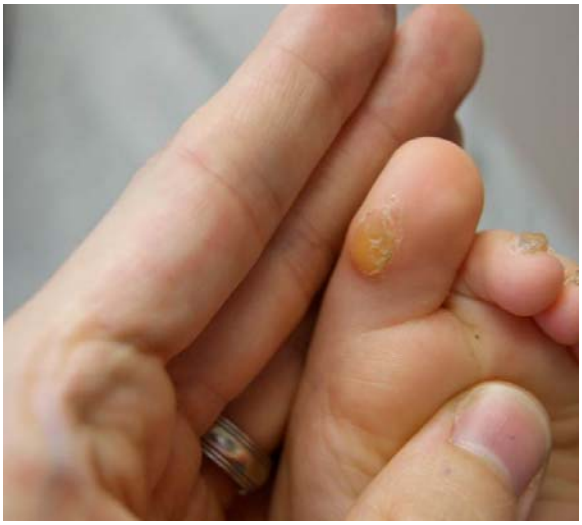
- Pathophysiology: Autosomal dominant inheritance of heterozygous mutations in any of keratins k6a (>50% of patients), k6b, k16, or k17 leads to fragility, cytolysis, and hyperkeratosis in tissues where those keratins are expressed. Identical missense mutations can produce very different phenotypes. There is higher likelihood of oral leukokeratosis in individuals harboring KRT6A mutations. Natal teeth and cysts are common in carriers of KRT17 mutations.

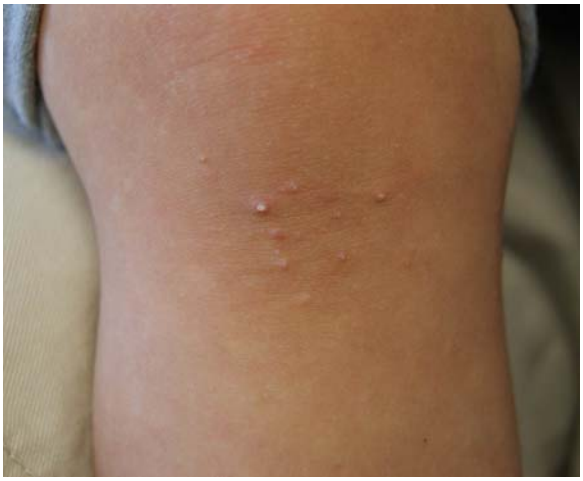
- Management: The most problematic symptom is painful focal PPK. Emollients, keratolytics, and rapamycin (oral) can be helpful.

- Nomenclature has changed: Type 1 (Jadasson-Lewandowsky) and Type 2 (Jackson-Sertoli) are no longer used. New nomenclature is based on the mutated keratin (ie. PC-6a, PC-17).

- This patient has Asn92Ser mutation in the KRT17 gene (PC-17). Her father is also affected.







Case 10: Familial Trichoepitheliomas

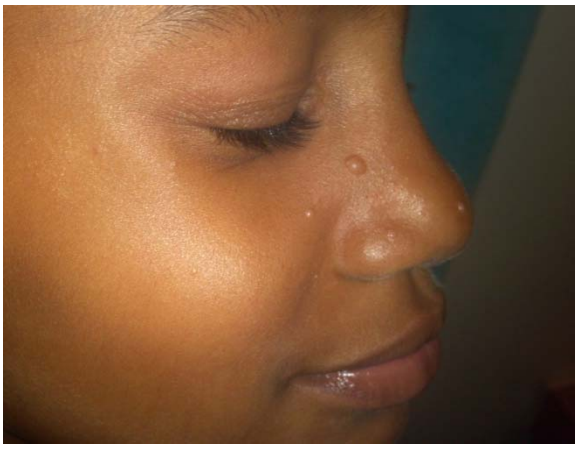
- Clinical Presentation: Skin-colored papules or small nodules predominantly in the nasolabial folds, but also on the nose, forehead, upper lip, and occasionally on the scalp, neck, and upper trunk. Onset is in adolescence with stabilization over time.

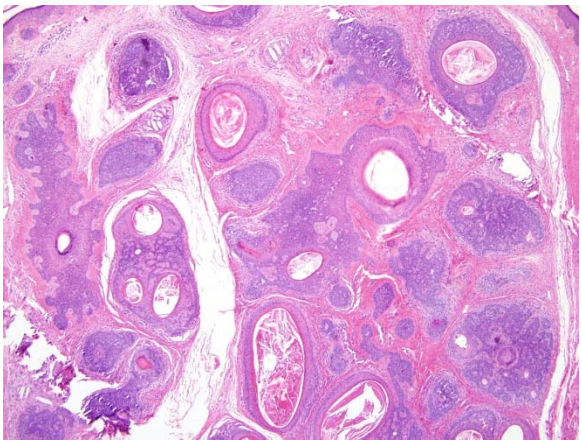
- Pathophysiology: Gene mutation originally mapped to chromosome 9p21. More recently, a frameshift mutation was found in Cylindromatosis gene (CYLD1), which is a negative regulator of nuclear factor kappa B (NF-κB) and critical for multiple signaling pathways. Mutated CYLD1 that has lost its deubiquitinating activity may contribute to oncogenesis by enhancing the degradation of proteins that suppress cell proliferation or promote apoptosis. Ultraviolet radiation has been suggested as major predisposing factor because of the characteristic distribution of trichoepitheliomas in sun exposed areas.

- Pathology: Clusters and cords of basaloid cells, papillary mesenchymal bodies, fibrocytic stroma.

- Malignant transformation is rare and controversial, but it has been reported.

- Allelic to Familial Cylindromatosis and Brooke-Spiegler Syndrome.





Case 11: Dominant Dystrophic Epidermolysis Bullosa

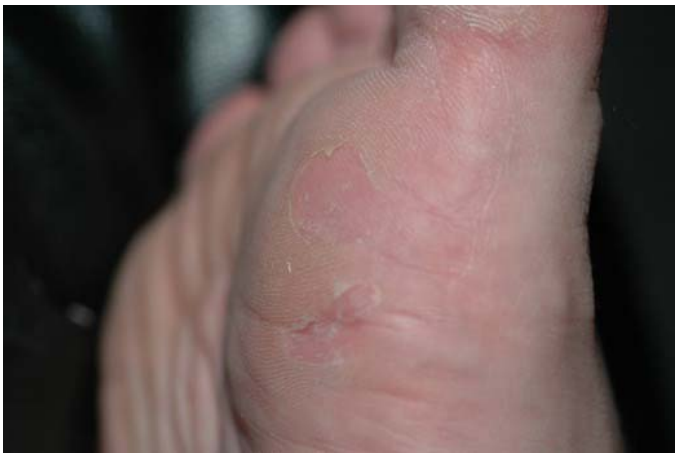
- Clinical Presentation: Mechanically fragile skin, blisters, and erosions usually limited to areas of trauma (hands, feet, knees, elbows). Atrophic scarring and milia. Due to depth of defect, it is difficult to mechanically induce blisters. Nail dystrophy.

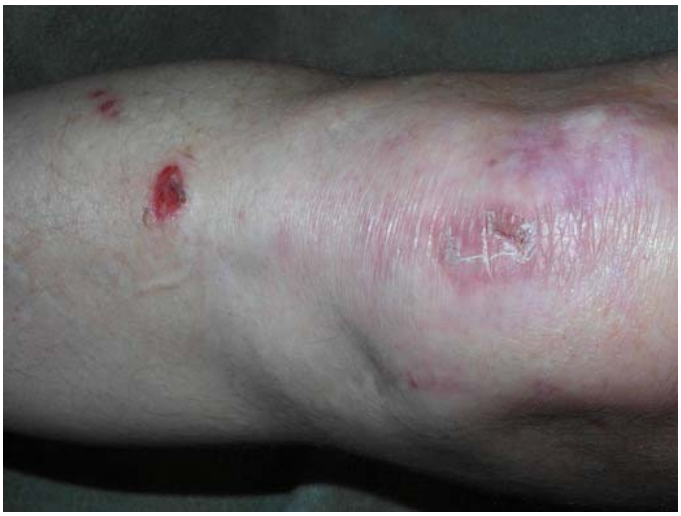
- Pathophysiology: Dominant negative mutation within the type VII collagen gene resulting in structurally abnormal protein with resultant mechanical fragility.

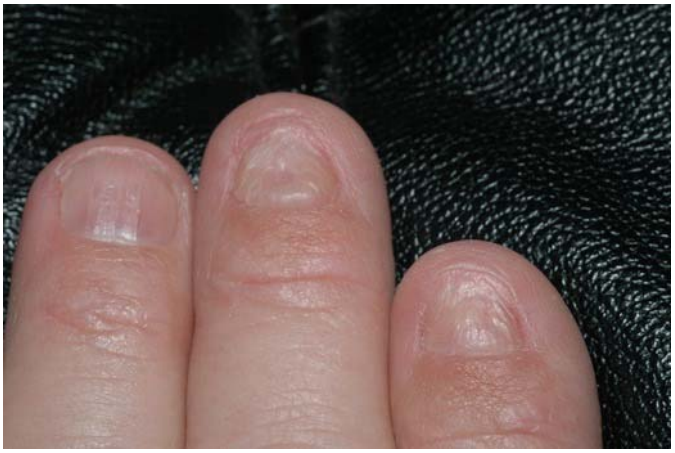
- Pathology: Transmission electron microscopy (TEM) identifies the ultrastructural level of blister formation. Immunofluorescence antigenic mapping distinguishes among subtypes by qualitative or semiquantitative expression of proteins. Blister formation occurs beneath the lamina densa. Anchoring fibrils appear normal in size and rudimentary structure, but are possibly reduced in number.

- Many subtypes are recognized, including pretibial, generalized, acral, nails only, and pruriginosa.

- Transient Bullous Dermatolysis of the Newborn: Mutations in type VII collagen gene, but blistering confined to the first 1-2 years of life. Usually dominant inheritance.







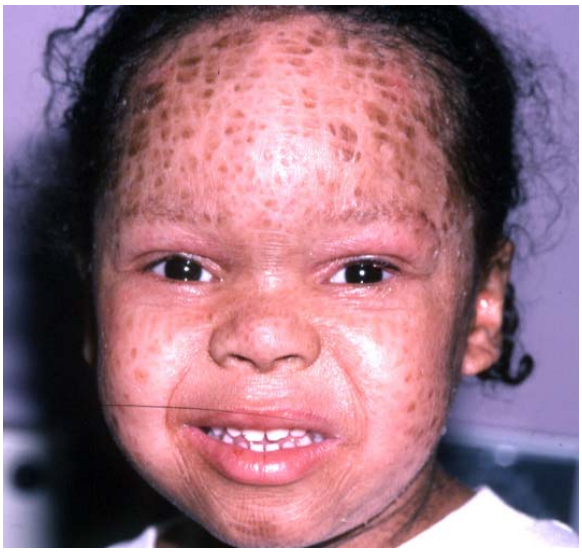
Case 12: Lamellar Ichthyosis

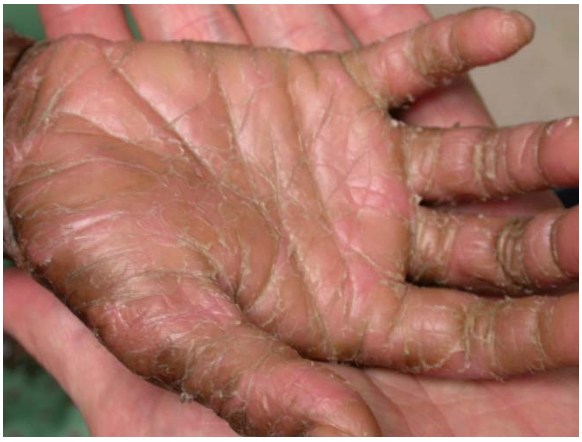
- Clinical Presentation: Collodion membrane at birth with underlying erythroderma, replaced by large, dark brown and plate-like scales. Ectropion and eclabium are common. Hypoplasia of nasal and auricular cartilage, scarring alopecia, nail dystrophy, and heat intolerance often occur; PPK is variable. Collodion membrane can be present in other congenital ichthyoses, so diagnosis is often not made until later in life.

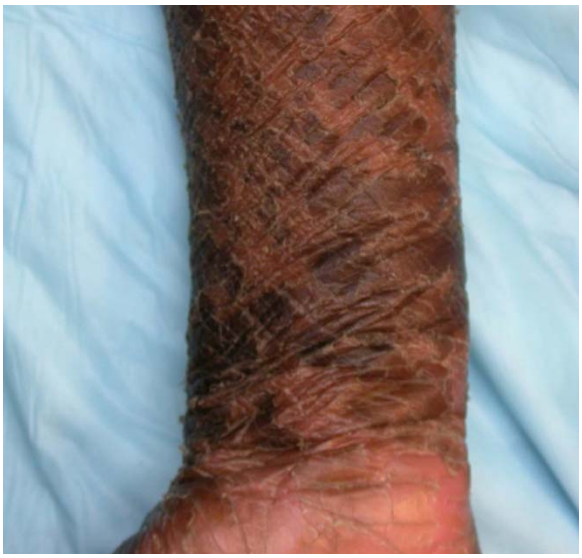
- Pathophysiology: Mutations in both copies of TGM1 gene leads to deficiency of transglutaminase-1, a protein expressed in the upper epidermis which is involved in formation of the insoluble protein envelope and attachment of the lipid envelope.

- Pathology: Non-diagnostic. Massive orthokeratotic hyperkeratosis over acanthotic epidermis.

- Treatment: Severe disease may necessitate systemic therapy with oral retinoids from early childhood. Topical management with vitamin D3 derivatives, tazarotene, lactic acid, and propylene glycol. May require ophthalmologic evaluation and surgical repair of ectropion to prevent irreversible corneal damage.

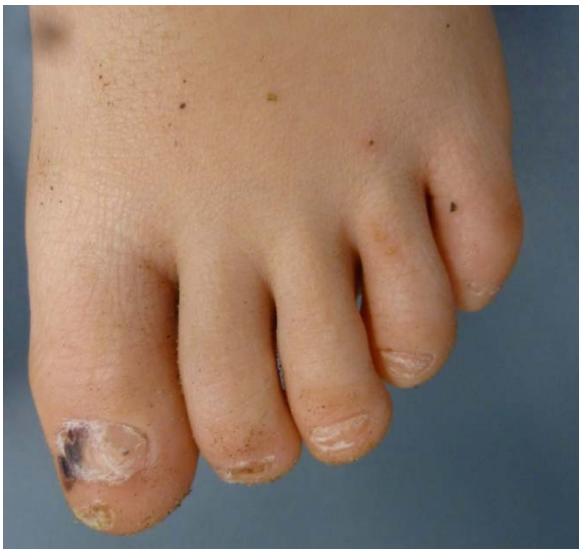






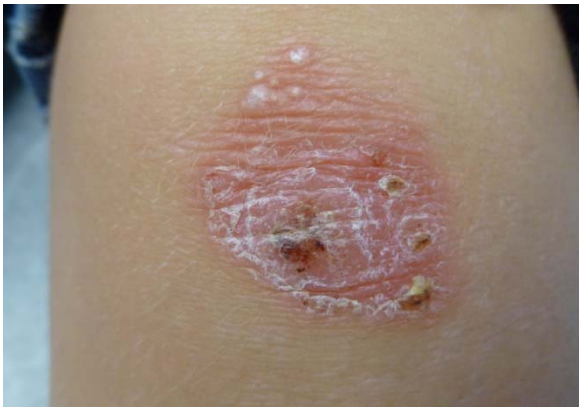
Case 13 & 14: Dominant Dystrophic Epidermolysis Bullosa

- Clinical Presentation: Patients usually present at birth, although milder versions may present later in life. Blisters typically affect the extensor extremities and the dorsum of the hands, which leave scarring and milia. Nail thickening, dystrophy, or complete nail destruction are common, particularly of the toenails. Teeth and hair are generally not affected.



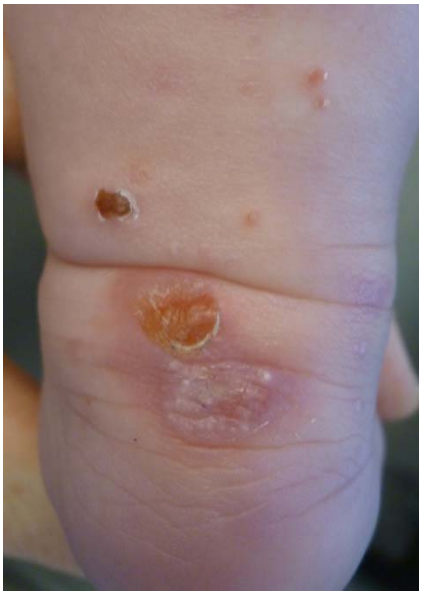
- Pathophysiology: Autosomal dominant mutations in type VII Collagen.

- Pathology: Traditional pathology does not help discern the level of the blister. Electron microscopy demonstrates a sub-lamina densa split, and sometimes diminished anchoring fibrils, while immunofluorescence shows normal or dereased expression of type VII collagen.



- Evaluation: About 20% of patients will have mucous membrane involvement, although it is mild and not problematic. There may be a slightly increased risk of basal cell carcinoma and melanoma.

- Subtypes include acral, which involves only the hands and feet; pretibial, which shows lichen planus-like lesions on the lower leg, and pruriginosa, which is unusually pruritic.



Case 15: Extensive Blaschkoid Epidermal Nevus

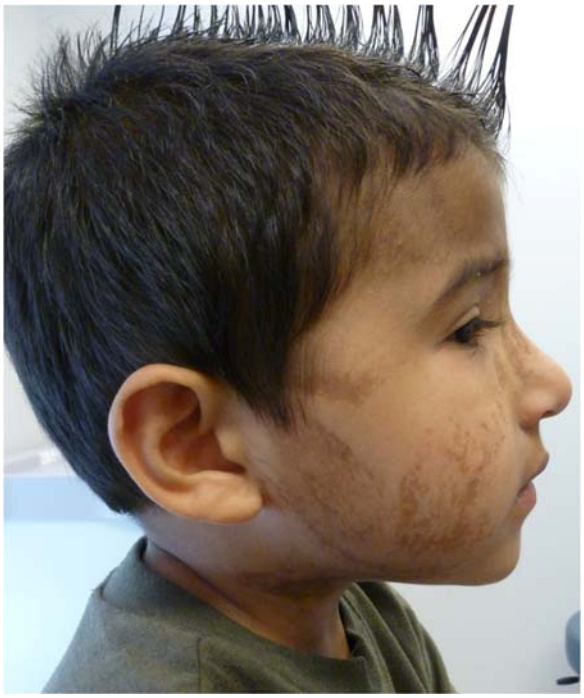
- Clinical Presentation: Asymptomatic, well-circumscribed, hyperpigmented macules, papules or plaques which follow the lines of Blaschko and stop abruptly at the midline, appearing within the first year of life. Some areas may have a verrucous appearance.

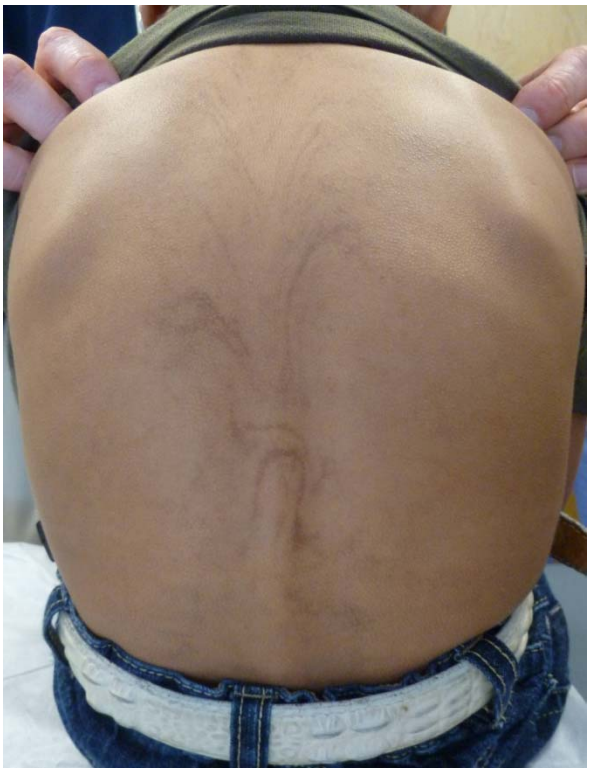
- Pathophysiology: There is genetic mosaicism of the epidermis and dermis. Mutations in fibroblast growth factor receptor 3 (FGFR3) have been identified.

- Pathology: Common findings include epidermal hyperplasia, hyperkeratosis, acanthosis, papillomatosis, and variable parakeratosis. Epidermolytic hyperkeratosis and focal acantholytic dyskeratosis are sometimes present.

- Evaluation: Consider Epidermal Nevus Syndrome, which most commonly involves neurologic or musculoskeletal anomalies (notably mutations in FGFR3 are associated with skeletal dysplasia). Although rare, cutaneous malignancies within epidermal nevi tend to occur around puberty.

- The differential diagnosis includes Inflammatory Linear Verrucous Epidermal Nevus (ILVEN) and lichen striatus.





Case 16: Neurofibromatosis Type 1

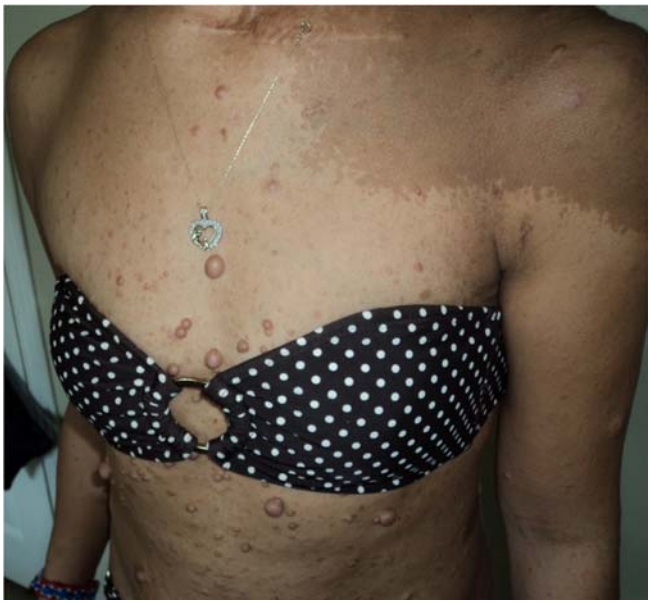
- Diagnostic Criteria: Two or More of the following:
  - ≥6 café au lait macules, which must be >5mm in prepuberty, >15mm postpuberty
  - ≥2 neurofibromas or 1 plexiform neurofibroma
  - axillary or inguinal freckling (Crowe's sign)
  - optic glioma
  - ≥2 Lisch nodules
  - sphenoid wing dysplasia or thinning of long bone cortex
  - first degree relative with NF1

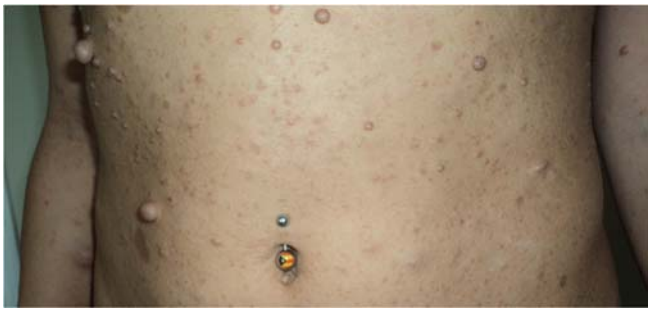
- Clinical Presentation: The café au lait macules are usually first to present, followed by axillary freckling, and then neurofibromas.

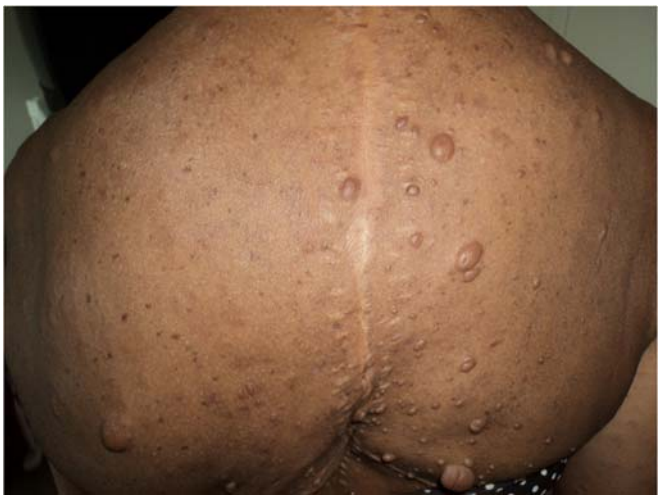
- Pathophysiology: Autosomal dominant mutations in the Neurofibromin (NF1) gene are responsible, but 50% of cases are due to sporadic mutations.

- Pathology: café au lait macules, neurofibromas, and plexiform neurofibromas have similar pathology to their sporadic counterparts.

- Evaluation: Annual ophthalmology and annual dermatologic exams. In particular, plexiform neurofibromas should be monitored; development of pain or neurologic symptoms could signal transformation to malignant peripheral nerve sheath tumor, which can be fatal.

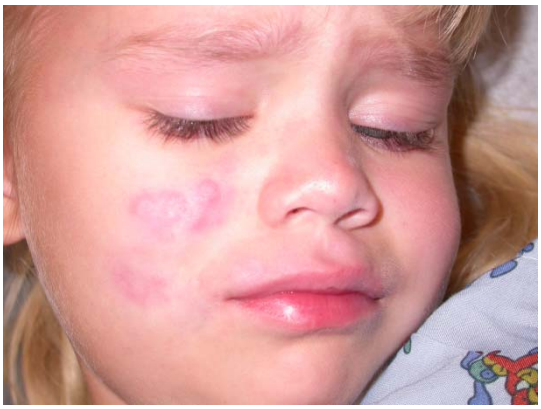




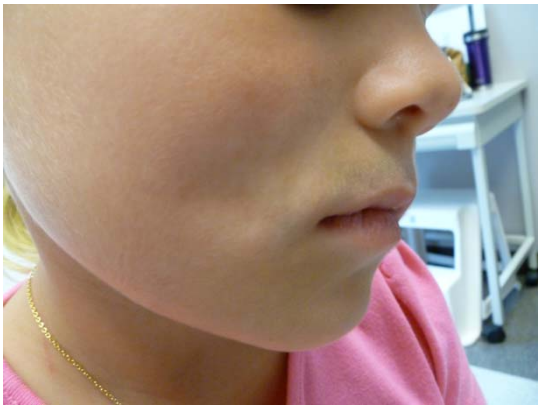


Case 17: Lupus Panniculitis

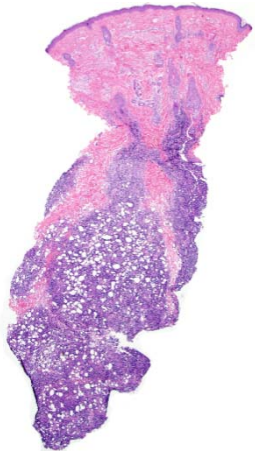
- Clinical Presentation: Crops of subcutaneous nodules and plaques on the face, proximal extremities, and trunk are classic. Changes in the overlying epidermis range from erythema or discoloration to the lesions of discoid lupus. Overlying skin often appears depressed, and lesions usually heal with subcutaneous atrophy.



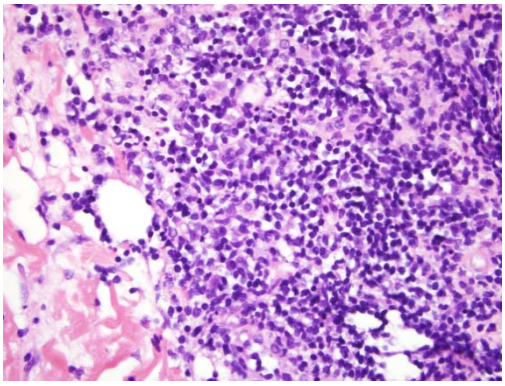
- Pathophysiology: The autoimmune basis is thought to be similar to that of other types of LE. Immunohistochemical analysis has shown an interferon-driven Th1-biased profile in active lesions.



- Pathology: Lobular or mixed lobular/septal panniculitis with hyaline necrosis and predominantly lymphoplasmacytic infiltrate. Mucin deposition and nodular aggregates of lymphocytes are also seen.



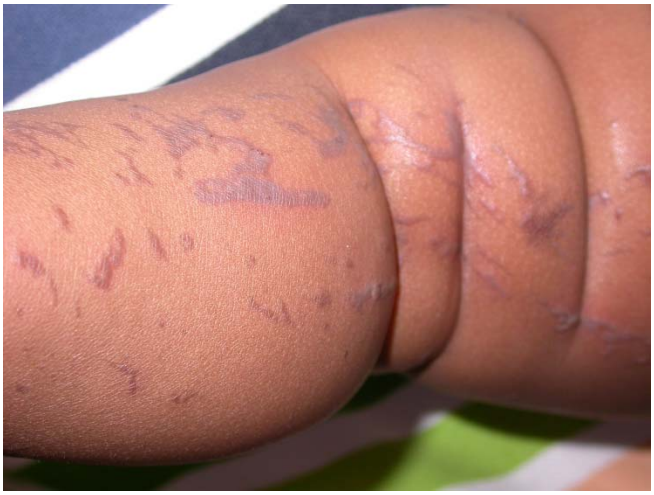
- Evaluation/Treatment: Associated with discoid lupus in at least 30% of patients and with SLE in 10-15% of patients. Recommend work-up with ANA, ENA, UA, CBC w/ diff, BUN/Cr, ESR, and complement levels. First-line treatment with antimalarials +/- systemic steroids in initial phase of disease. Overlying discoid lesions treated with potent topical or intralesional steroids.



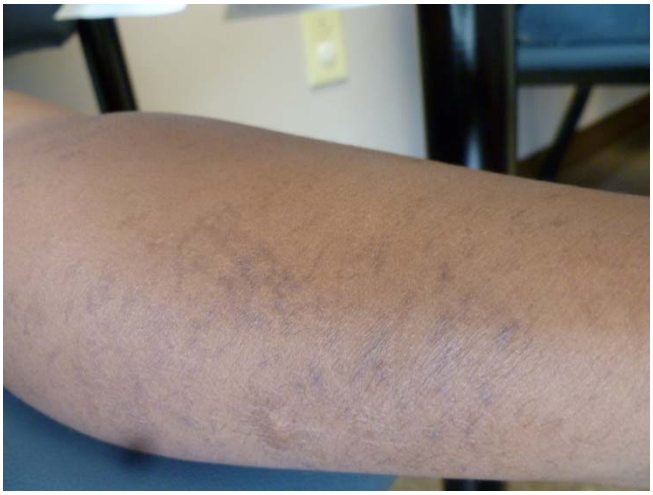
- Similar pathology has been seen in cases of subcutaneous panniculitis-like T-cell lymphoma. T-cell receptor gene rearrangement studies are helpful. Patients should be followed over time.

Case 18: Incontinentia Pigmenti

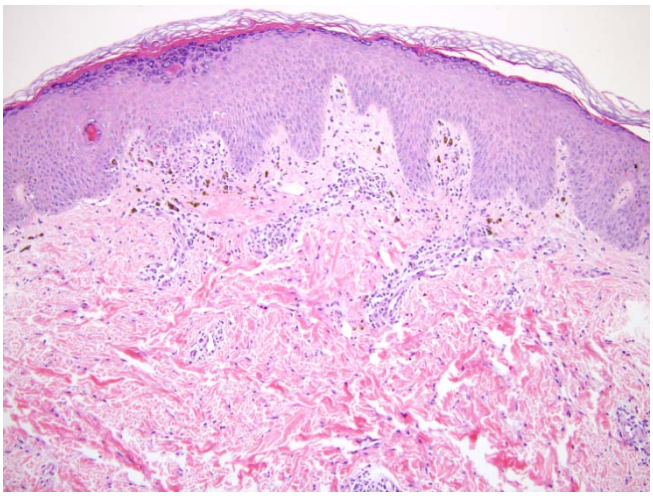
- Clinical Presentation: Classically, female infants present with skin lesions following Blaschko's lines. Four stages that often overlap: inflammatory/ vesicular (first 2 months), verrucous (2-6 months), hyperpigmented (> 6 months), and hypopigmented (adolescence and on). Lesions favor extremities and rarely affect the face. Other ectodermal abnormalities include alopecia, nail dystrophy, and pegged or missing teeth. Patient may also have ocular and CNS abnormalities.



- Pathophysiology: X-linked dominant disorder due to mutations in the NEMO (IKBKG) gene at Xq28. The NEMO protein is a kinase subunit that activates NF-κB, a transcription factor that protects against TNF-α-induced apoptosis. Thus, the NEMO mutation creates a pro-apoptotic state.



- Pathology: Inflammatory vesicles show eosinophilic spongiosis and dyskeratotic keratinocytes. In verrucous lesions there is acanthosis with hyperkeratosis and foci of dyskeratosis. In stage 3, there is pigmentary incontinence and variable vacuolization of basal keratinocytes. Stage 4 is characterized by a thinned epidermis and dermis devoid of adnexa.



- Evaluation: Refer to ophthalmology, neurology, and genetics. Dental exams are also important. Mother should be examined for areas of atrophy, alopecia, and hypopigemenation, and questioned about tooth loss at an early age.

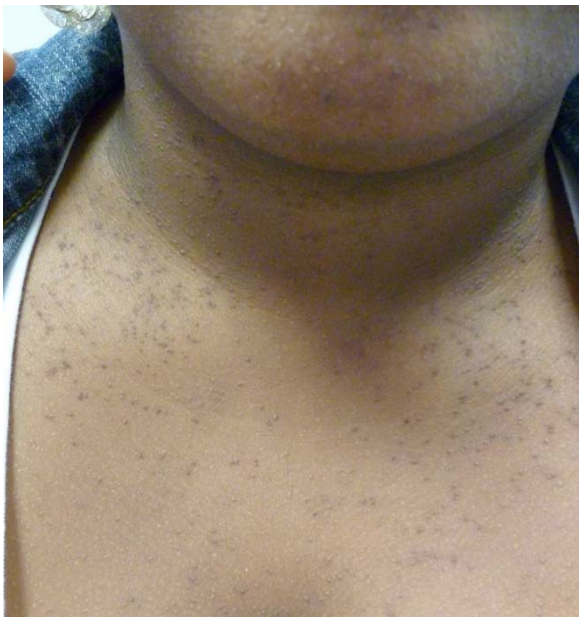
Case 19: Darier's Disease

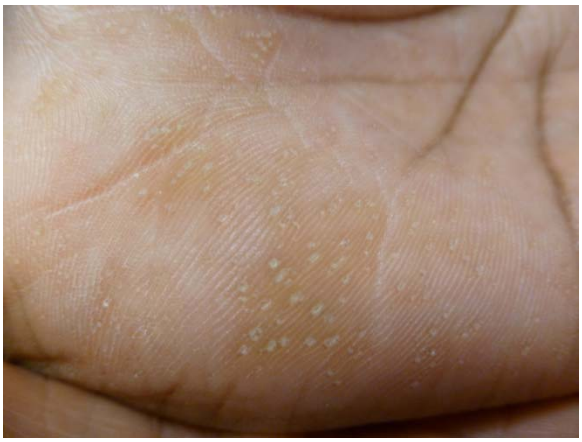
- Clinical Presentation: Disease onset between 6-20 years in ~70% of patients with peak during puberty. Primary lesions are keratotic red-brown papules in seborrheic distribution. Palmoplantar keratotic papules and pits as well as nail changes, including longitudinal red and white bands, ridging, wedge-shaped subungual hyperkeratosis, and brittle, broken nails with distal V-shaped notches are characteristic. Subtypes include acral hemorrhagic variant and segmental forms.

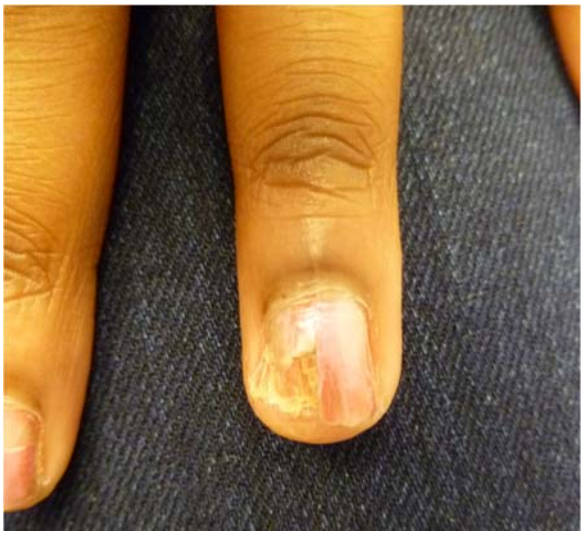
- Pathophysiology: Autosomal dominant inheritance of a mutation in the ATP2A2 gene, which encodes an endoplasmic reticulum Ca^{2+} ATPase, SERCA2. This results in dysfunctional intracellular calcium signaling causing apoptosis and acantholysis through mechanisms not entirely understood, but possibly related to the synthesis, processing, folding, and trafficking of junctional proteins.

- Pathology: The two prominent histologic features are acantholysis with suprabasilar clefting and dyskeratosis, with corps ronds and grains described.

- Evaluation/Treatment: Confirm the diagnosis with family history or biopsy. Basic management with lightweight clothing, sunscreen, antimicrobial cleansers, and keratolytic emollients. Treatment traditionally with combination of topical steroids and retinoids or systemic retinoids in severe cases. Consider topical 5-FU or lasers.

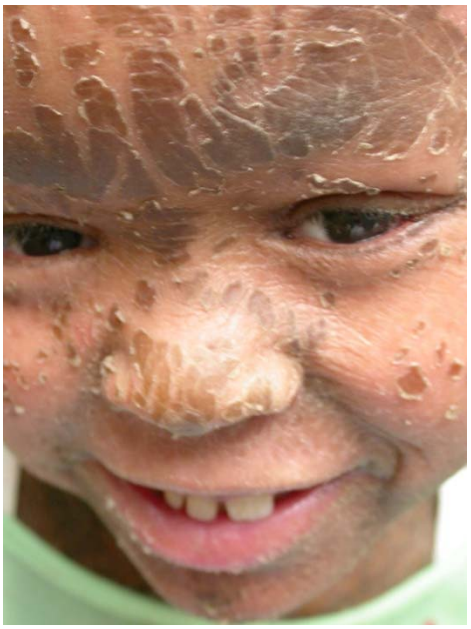




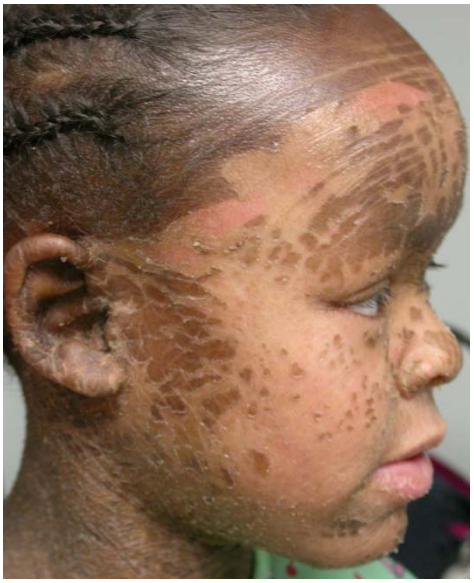


Case 20: Lamellar Ichthyosis

- Clinical Presentation: The hallmark is a collodion membrane at birth. Over the first few weeks, this membrane is shed revealing transient erosions that are replaced by generalized large, brown, plate-like scales that form a mosaic or bark-like pattern with minimal to no associated erythroderma. Prominent flexural involvement and superficial fissures often seen. Ectropion, eclabium, and scarring alopecia are also common.



- Pathophysiology: Inherited autosomal recessive (rare autosomal dominant) disorder most often due to mutations in the TGM1 gene, resulting in transglutaminase-1 enzyme deficiency. This enzyme normally facilitates the formation of the cornified cell envelope by cross-linking structural proteins to each other and to the lipid envelope. Missense mutations in ABCA12 gene, a copper binding protein, are also reported in those of Northern African descent.



- Pathology: Histologic abnormalities are not diagnostic. Massive orthokeratotic hyperkeratosis with an acanthotic epidermis; psoriasiform or papillomatous hyperplasia is often seen.

- Evaluation/Treatment: Referral to genetics and ophthalmology for genetic testing/counseling and management of ectropion. Topical treatment with vitamin D_3 derivatives, tazarotene, lactic acid and propylene glycol formulations. Systemic treatment with retinoids is often necessary.

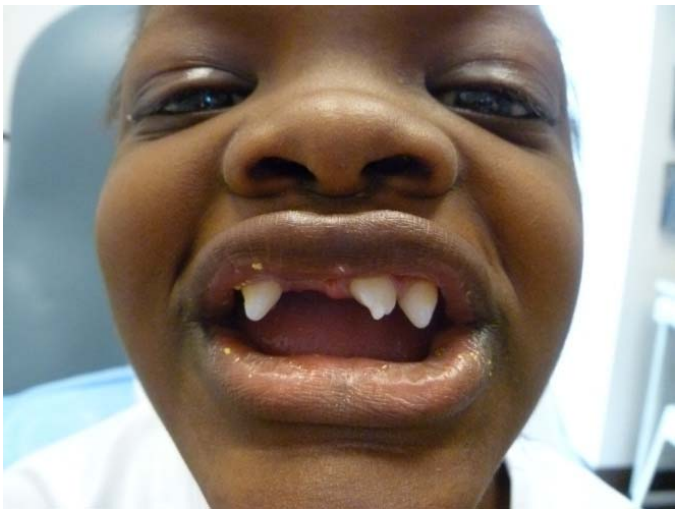
Case 21 & 22: X-linked Anhidrotic Ectodermal Dysplasia

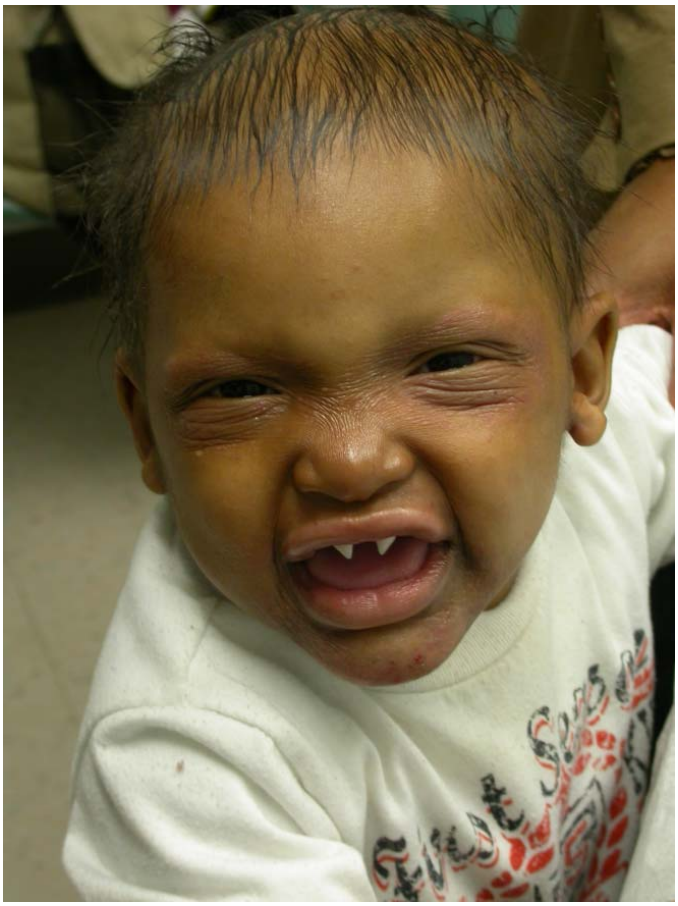
- Clinical Presentation: Presents in early infancy with eczema, conical teeth, sparse hair (especially eyebrows) and hypohidrosis. Some difficulties with recurrent respiratory tract infections. Gene testing confirmed diagnosis in our patients. Periocular wrinkling is an early clue, and collodion membrane may be present at birth.

- Pathophysiology: Arises from mutations in ectodysplasin and ectodysplasin receptor genes (EDA, EDAR, and EDARADD) which code proteins participating in the signaling pathways between embryonic ectoderm and mesoderm. Most common inheritance is X-linked with an overall incidence of 1-7/100,000, although rare autosomal dominant and recessive forms exist.

- Evaluation/Management: Panorex films of the jaw can be helpful as they can reveal multiple absent or malformed teeth. Gene testing for EDA1 gene for X-linked type is available.

- It is important to avoid overheating; use air conditioning, wet shirts or spray water bottles for sports. Lubrication and humidifiers are helpful to keep secretions in eyes, nose, throat and ears loose and moist thereby minimizing infection. Early dental intervention can help prevent everted lips. Carriers may show signs so examine parents.





Case 23: Lymphedema Dystichiasis Syndrome

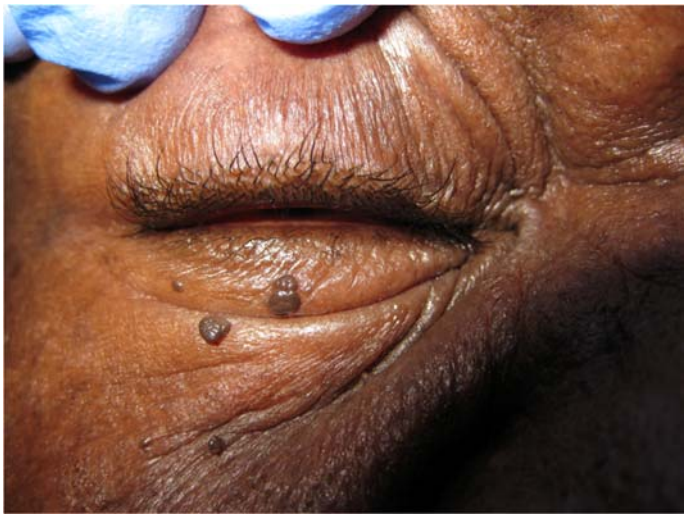
- Clinical Presentation: Presents with lower limb lymphedema and distichiasis (aberrant eyelashes ranging from a full set of extra eyelashes to a single hair). Ocular complications are frequent and include corneal irritation and recurrent conjunctivitis. Also common are varicose veins, congenital heart disease, and ptosis.

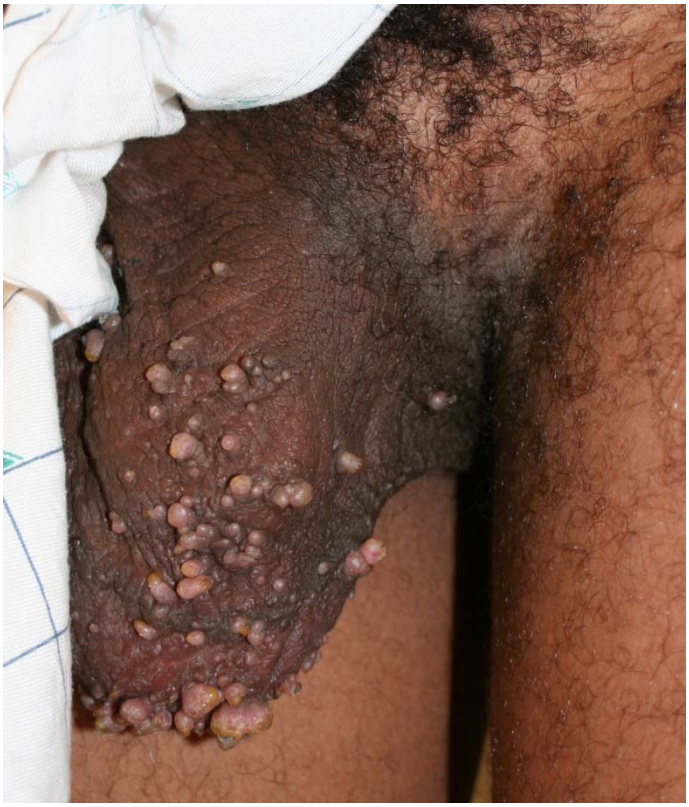
- Pathophysiology: Autosomal dominantly inherited mutation in the FOXC2 gene transcription factor located on 16q24.1, thought to play a critical role in fetal development of the lymphatic and cardiovascular systems, among others.

- Diagnosis: Genetic testing.

- Evaluation/Management: Fetal echocardiography is recommended because of the increased risk for congenital heart disease. Lubrication and eyelash removal (plucking, electrolysis) can reduce corneal irritation. For lymphedema, compression stockings and referral to wound care clinic if needed.

- This case presented with history of congestive heart failure, 20 years of chronic lymphedema and 'genital warts'. Exam revealed bilateral double rows of eyelashes and scrotal lymphangiectasias.

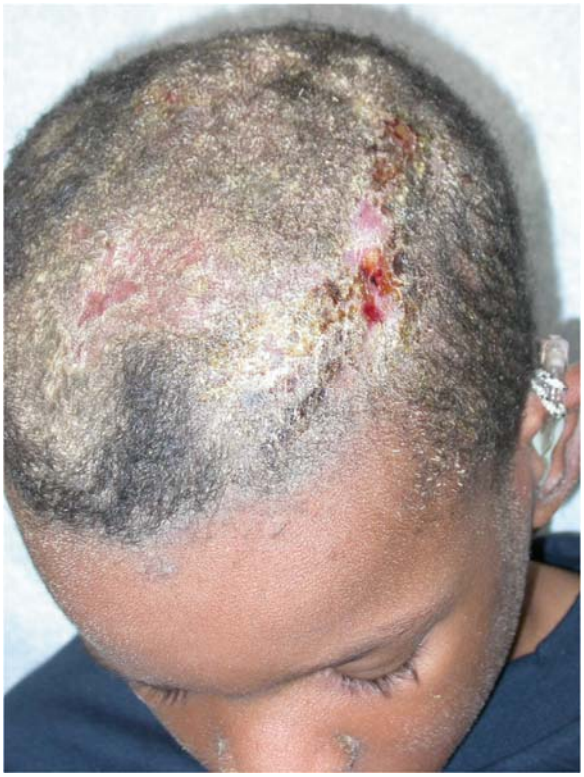




Example image of lymphangiectasias: http://dermatlas.med.jhmi.edu/derm/indexDisplay.cfm?ImageID=681319267 accessed 9/15/12

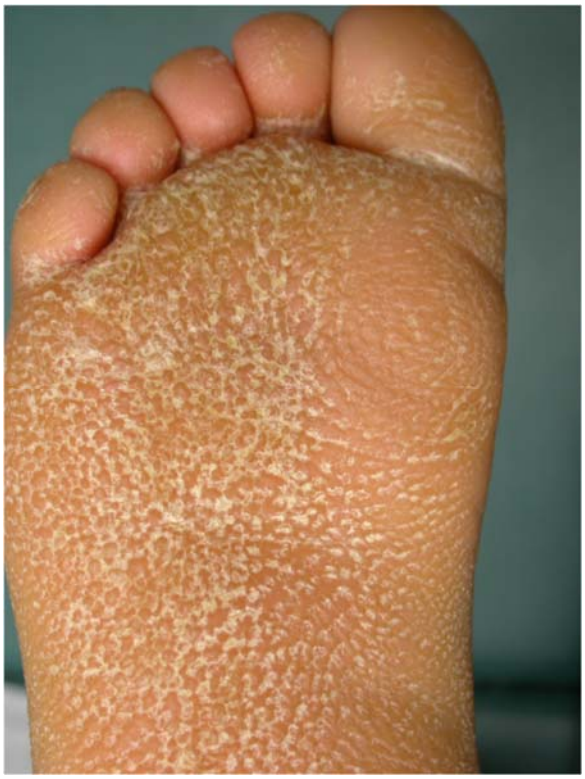
Case 24: KID Syndrome

- Clinical Presentation: *K*eratitis [progressive inflammation and thickening of the cornea (vascularizing keratitis) that may not present until later]; *I*chthyosis (diffuse erythema and fine scale in infancy evolves to erythrohyperkeratotic verrucous plaques, predominantly on the face and limbs, stippled palmoplantar keratoderma, and sparse or absent hair); *D*eafness (congenital non-progressive neurosensory hearing loss).



- Pathophysiology: Autosomal dominant mutation in gap junction beta 2 (GJB2) gene on chromosome 13 coding for connexin 26, which is involved in intercellular communication in the cochlea and epidermis. Gene testing is available.

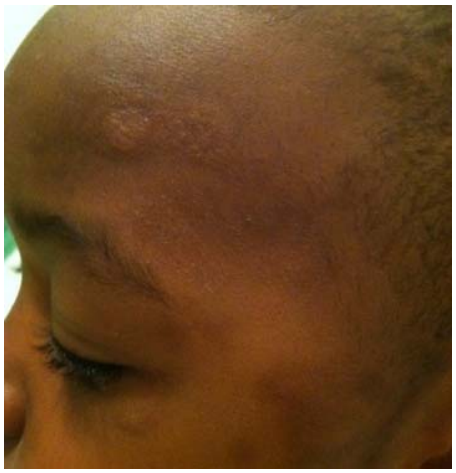
- Management: Hearing aids, speech therapy, and early intervention important to promoting normal development. Good candidates for cochlear implants, but skin-related complications can disrupt post implantation healing. Systemic retinoids produce mixed results. Retained hyperkeratosis can be ideal environment for recalcitrant fungal and bacterial colonization.



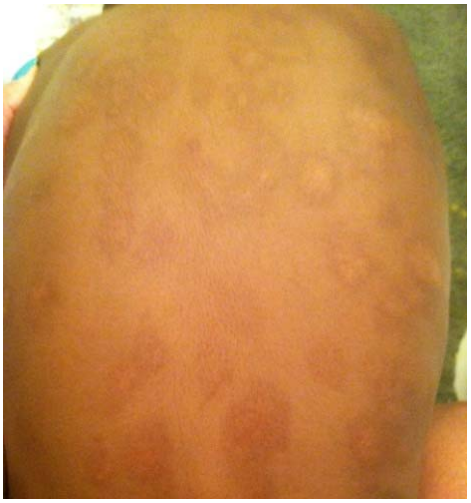
- This case was diagnosed at birth with abnormal nails and at 8 months with hearing loss. Gene testing confirmed KID. Presented initially to dermatology with recurrent fungal and bacterial infections, especially involving the scalp.

Case 25: Urticaria Pigmentosa

- Clinical Presentation: Erythematous to brown macules and papules which urticate upon stroking (Darier's sign). Onset is typically within the first year of life and the natural history is resolution by puberty. In addition to pruritus, flushing, blistering and other skin symptoms, there may also be associated GI symptoms such as diarrhea and abdominal pain.

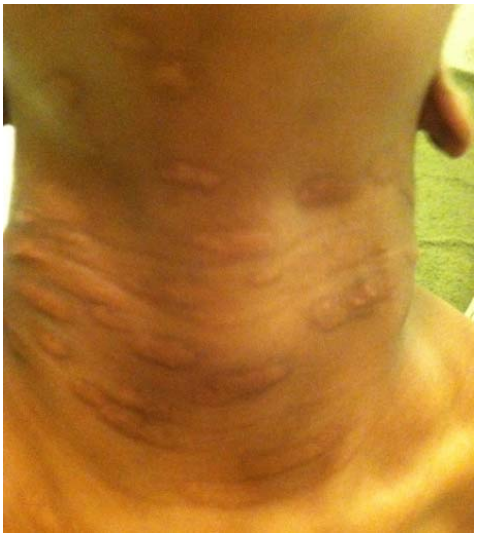


- Pathophysiology: Most common presentation of cutaneous mastocytosis. Cutaneous mast cells may have c-kit mutations, but bone marrow mast cells do not.



- Pathology: Increased numbers of mast cells in the papillary dermis, often in a perivascular distribution.

- Evaluation: Serum tryptase to screen for systemic involvement. If serum tryptase is elevated or lesions persist beyond puberty, then consider bone marrow biopsy.



- Management: Avoidance of histamine releasing triggers such as mechanical stimuli, medications (NSAIDs, opiates, vancomycin), and hymenoptera stings. Topical corticosteroids, antihistamines, and cromolyn sodium may reduce symptoms.

Case 26: Parry-Romberg Syndrome

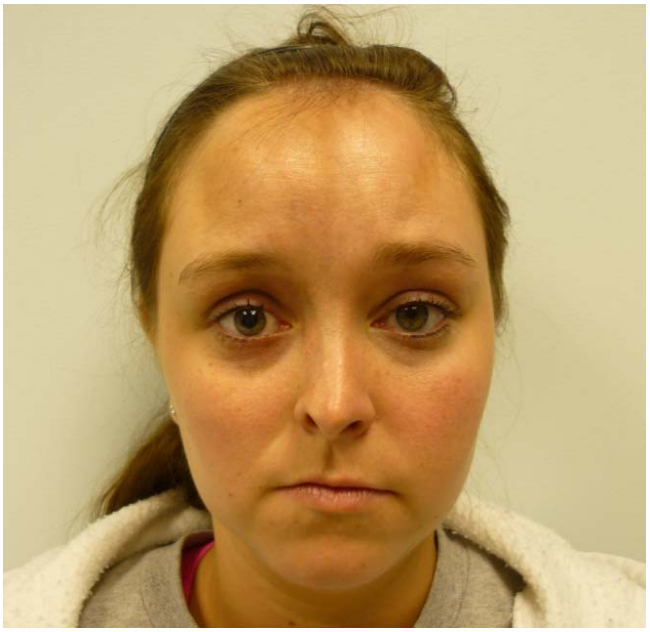
- Clinical Presentation: Slow, progressive atrophy of the subcutaneous fat, muscle and rarely bones of the face. Almost always unilateral. Typically begins in the 1st or 2nd decade of life and is more common in females.

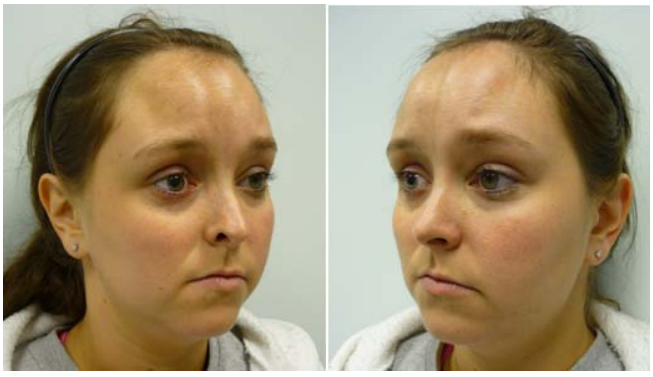
- Pathophysiology: Idiopathic but many feel that it represents a severe subtype of linear morphea. Many patients have high ANA titers.

- Evaluation: Dental and ophthalmological examination. MRI of the brain in patients with seizures.

- Management: Medications may include immunomodulators such as methotrexate, corticosteroids, and hydroxychloroquine in the active phase. Surgical management can include autologous fat transfer and dermal fillers for aesthetic improvement.

- Up to 10% may have bilateral involvement. Trigeminal neuralgia, Horner's syndrome, uveitis, and dental abnormalities, among other complications, may occur.





Different pt: Pre- and post 3 stages of grafting

Case 27: Basal Cell Nevus Syndrome

- Clinical Presentation: Multiple basal cell carcinomas, odontogenic cysts, palmar or plantar pits, calcification of the falx cerebri, bifid ribs, frontal bossing, hypertelorism, broad nasal root, and medulloblastoma (see residua on the MRI at right).

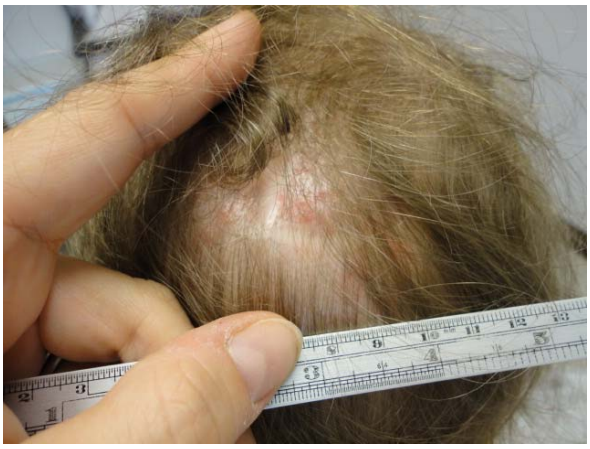
- Pathophysiology: Autosomal dominant. Due to a mutation in the patched genes (PTCH 1 or 2).

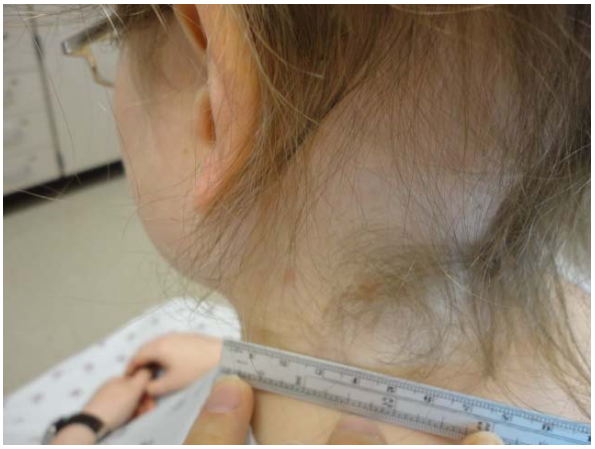
- Evaluation: Radiographs of the skull, jaw and chest.

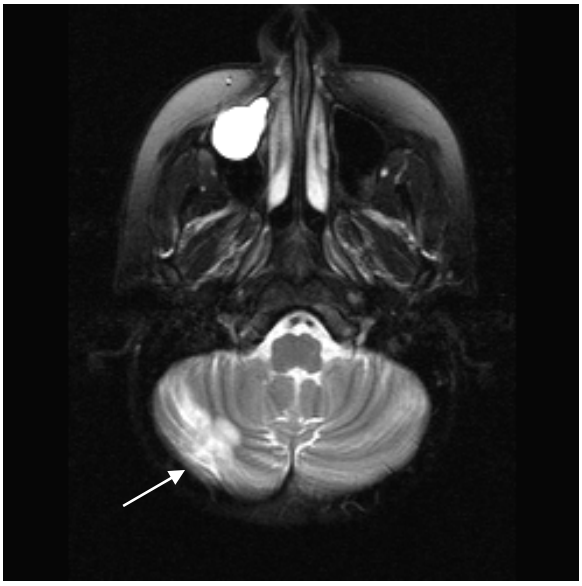
- Management: Minimize radiation exposure as this can lead to increased tumor growth, as in our patient who received radiation therapy of the head and neck for treatment of her medulloblastoma.

- Treatment options include topical 5-FU, imiquimod, topical retinoids, and photodynamic therapy in addition to standard options such as excision, cryosurgery and ED&C.

- Vismodegib, an orally administered smoothened inhibitor, was FDA approved in January 2012. Frequent side effects include alopecia, dysgeusia, and muscle cramps.







Changes following treatment of a medulloblastoma in the posterior fossa

Case 28: Epidermolysis Bullosa Simplex, Dowling-Meara Subtype with EB Nevi

- Clinical Presentation: The most severe subtype of EB simplex. Blisters often occur in a grouped (herpetiform) or arcuate array. Repeated blistering of the palms and soles can lead to keratoderma. Involvement of oral mucosa, nail dystrophy, and milia formation are frequently seen.

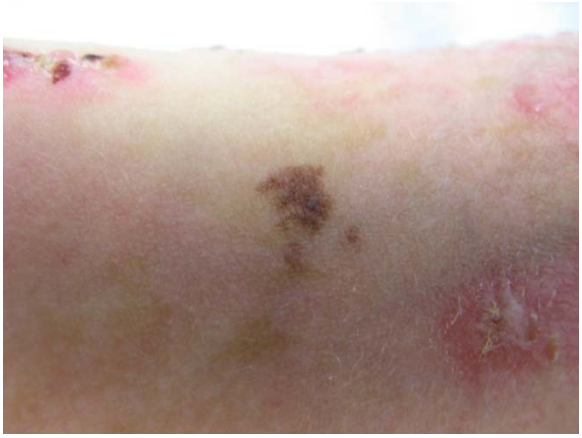
- Pathophysiology: Autosomal dominant condition due to mutations in genes encoding keratins 5 or 14.

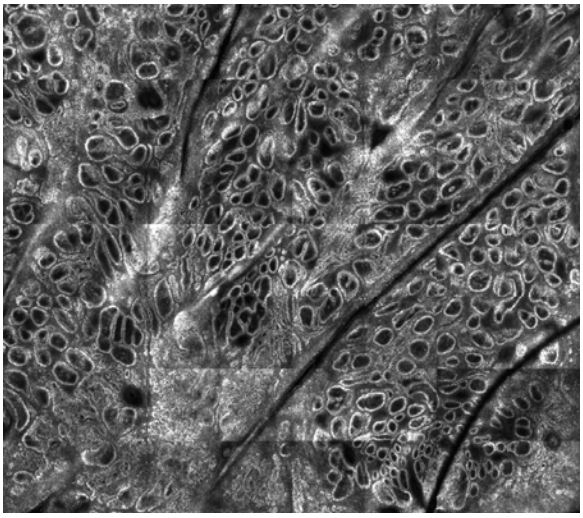
- Pathology: Electron microscopy will reveal intrakeratinocyte cleavage and clumped intracytoplasmic keratin filaments (tonofilaments).

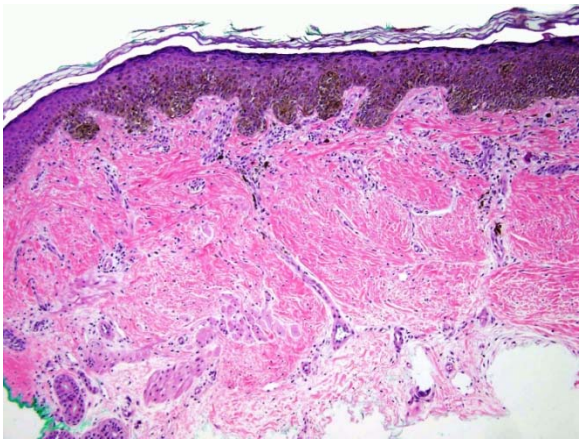
- Management: Supportive care. Minimize trauma/pressure to prevent blisters. Avoid high temperatures and humid environments. Bleach baths and topical antibiotics to prevent infection.

- Most patients have a normal lifespan. Many experience decreased blister activity in adulthood.

- Large, eruptive melanocytic nevi have been reported at sites of repeated blistering. These often appear asymmetric with irregular pigmentation. To date no cases of malignant transformation have been reported.







Case 29: Granulomatous Cheilitis with Crohn's Disease

- Clinical Presentation: Progressive, intermittent swelling eventually becoming persistent and causing permanently enlarged lips.

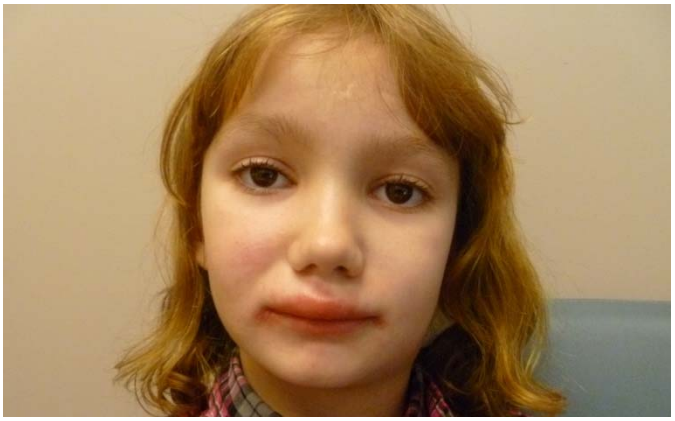
- Pathophysiology: Th1- and Th17-mediated granulomatous cutaneous inflammation associated with underlying Crohn's disease.

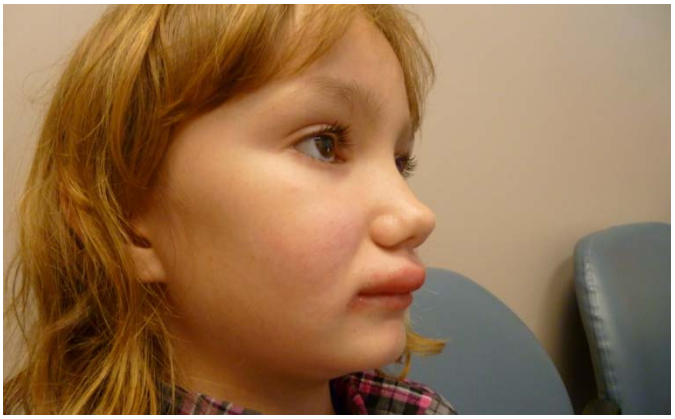
- Pathology: Marked edema in the dermis. Focal, non-necrotizing granulomas (collections of epithelioid histiocytes and giant cells) with surrounding lymphocytes and plasma cells.

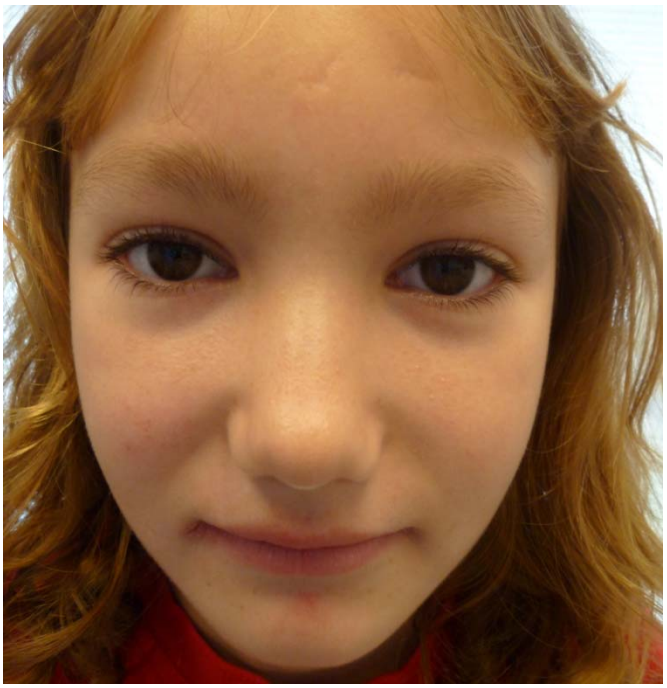
- Evaluation: Given this diagnosis is a possible first manifestation of Crohn's disease, obtain an in-depth review of systems and consider referral to GI for workup. Examine for perianal involvement.

- Treatment: Intralesional corticosteroids have been effective for some. Infliximab, used to treat the GI manifestations of Crohn's, has also been shown to be successful in treating granulomatous cheilitis associated with the disease.

- Our patient first manifested with granulomatous cheilitis. After being worked up by GI, she was found to have Crohn's disease based on colonoscopy and histological findings. Her lip swelling has resolved with the initiation of infliximab.







After treatment with infliximab

Case 30: Enberger-like Syndrome

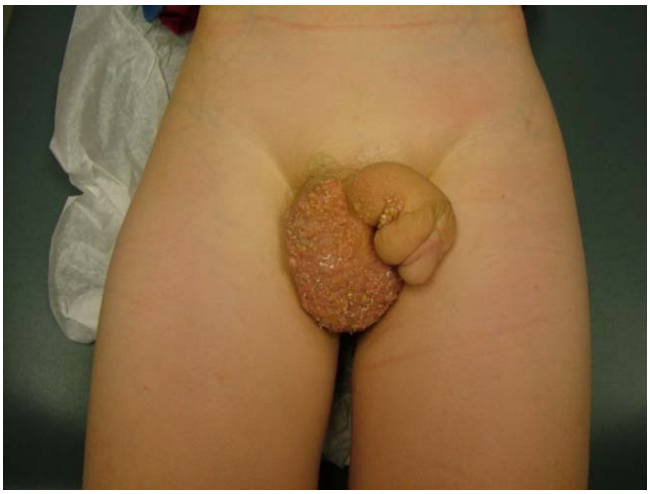
- Clinical Presentation: Presented with bilateral, firm, non-pitting edema of the lower extremities, penile and scrotal edema, and innumerable verrucous papules, some weeping clear fluid.

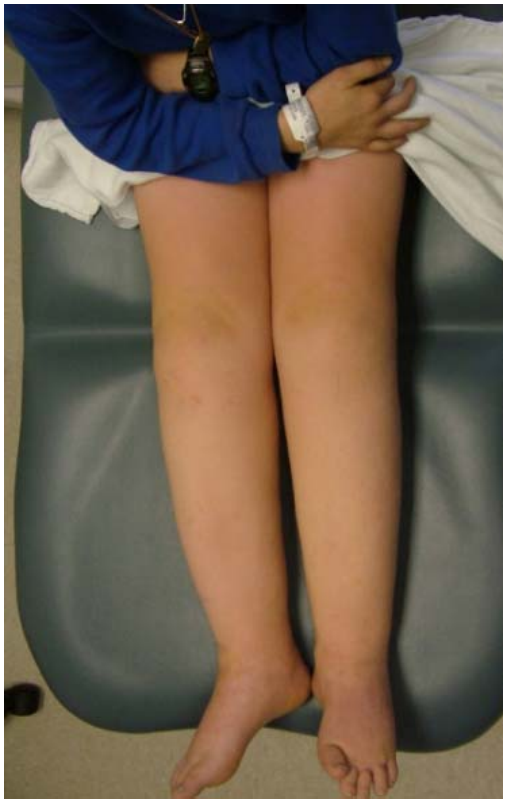
- Pathophysiology: Emberger syndrome is thought to be caused by a mutation in GATA2, which is normally expressed in hematopoietic stem cells. It plays an important role in the development and maintenance of the lymphatics and heme system. The inheritance pattern is unclear, but it is thought to be AD with variable penetrance and expression.

- Pathology of lymphangiectasia: Vascular ectasia with surrounding epidermal hyperplasia with hyperkeratosis

- Evaluation: Emberger syndrome is primary lymphedema associated with myelodysplasia. Lymphedema typically precedes pancytopenia or myelodysplasia, which eventually progresses to AML. There is increased incidence of chromosome 7 monosomy in the bone marrow. Patients should be monitored with serial CBCs or followed by a hematologist/oncologist. Other findings include epicanthic folds, hypertelorism, sensorineural deafness, neck webbing, multiple warts, and long, slender fingers.

- While genetic testing for Emberger syndrome in our patient is negative, his presentation of lower extremity and genital lymphedema closely resembles this syndrome. Our patient has microcephaly and chromosome abnormalities on genetic testing, but does not fit into a specific syndrome. His lymphedema has been treated with rapamycin, erbium YAG laser, and aggressive OT with massage and customized compression stockings.





Case 31: Piebaldism

- Clinical Presentation: Patients typically have white forelock in midline of frontal scalp and patchy absence of pigment, with areas of normal pigment and hyperpigmentation within, located on trunk and mid-extremities. Depigmentation can involve medial eyebrows and eyelashes.

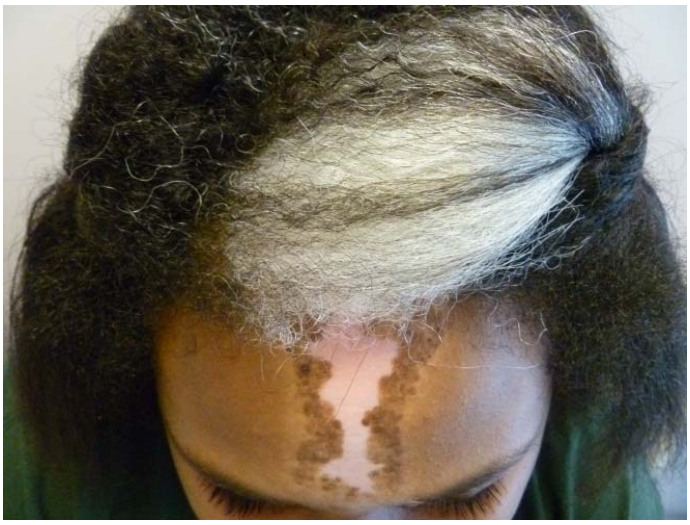
- Pathophysiology: Autosomal dominant mutation in the KIT gene on chromosome 4q11-12, which encodes a cell surface receptor for the KIT ligand, Steel Factor (an embryonic growth factor). Stimulation of this receptor is required for normal development of melanocytes/blasts.

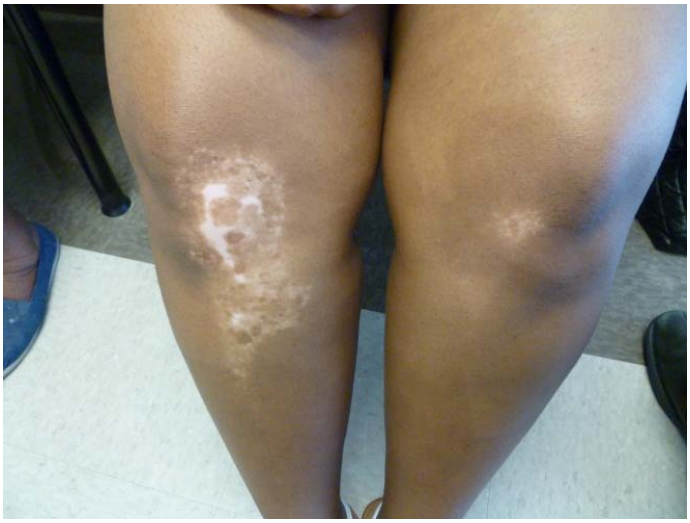
- Pathology: Absence of melanocytes in epidermis or hair follicles. May see increased melanosomes in histologic specimens from hyperpigmented areas.

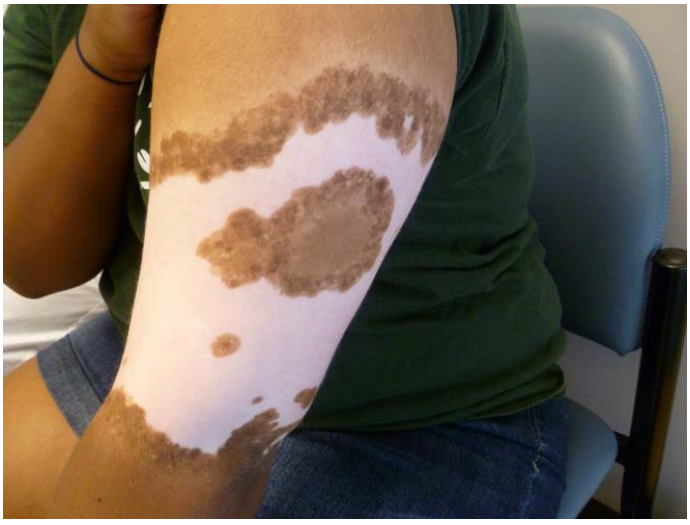
- Associated conditions: Hirschsprung disease is rarely associated with piebaldism, likely because enteric ganglion cells are derived from the neural crest and thus, like melanocytes, develop aberrantly.

- The white forelock is present in 80-90% of patients and can be diamond or triangular shaped. Patients are typically healthy and without the visual or auditory symptoms seen in patients with other hereditary melanocytic disorders.

- This patient's father and 3 of her 7 siblings are similarly affected.







Case 32: Muir-Torre Syndrome

- Clinical Presentation: Sebaceous tumors (listed below) and/or keratoacanthomas in association with internal malignancy.
  - Sebaceous hyperplasia: skin-colored to yellow, umbilicated papules
  - Sebaceous adenoma: pink, flesh colored, or yellow papule or nodule.
  - Sebaceoma: yellow or orange papules, nodules, or plaques
  - Sebaceous carcinoma: yellow/pink, painless nodule, usually on face or trunk

- Pathophysiology: Subset of Hereditary Nonpolyposis Colorectal Cancer Syndome. Mutation in DNA mismatch repair gene (MLH1, MSH2, MSH6), which leads to microsatellite instability.

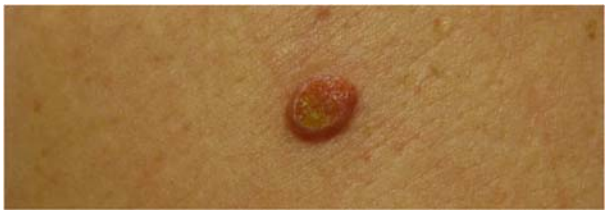
- Pathology: In addition to typical pathology findings of the lesions above, Muir-Torre is more likely to be associated with cystic sebaceous tumor and seboacanthoma.
  Cystic sebaceous tumor: well-circumscribed cystic neoplasm with cyst wall composed of immature basaloid cells and filled with homogenous eosinophilic material in deep dermis or subcutaneous tissue.
  Seboacanthoma: Architecture of a KA but with well-differentiated sebaceous lobules.

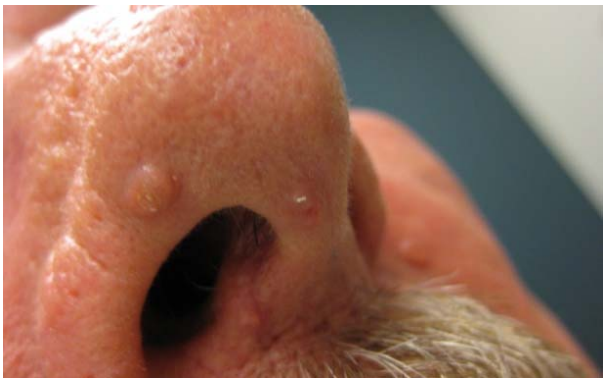
- Evaluation: Diagnosis based on:
  - Sebaceous tumor or KA with sebaceous differentiation + internal malignancy, or
  - Multiple KAs + internal malignancy + Family history of Muir-Torre

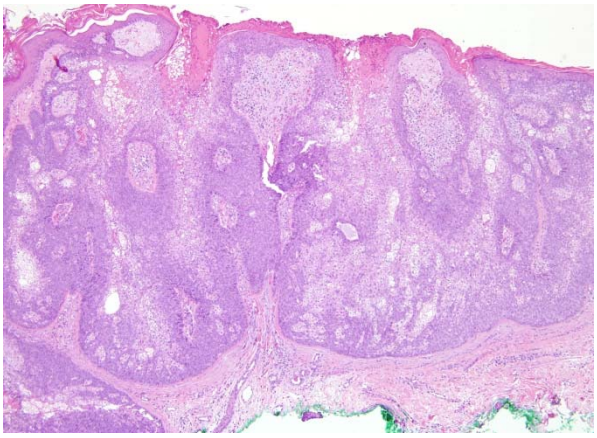
- Patients must be screened for GU and GI malignancies beginning at even younger ages. Colonoscopies beginning at age 20-25, serial urinalyses and CBCs, annual breast and pelvic exams with consideration for transvaginal ultrasound.

- Muir-Torre syndrome is associated with increased risk of colonic adenocarcinoma, GU tumors, breast cancer, heme malignancies, head & neck cancers, and small intestinal cancers.

- Our patient presented with one KA on his back, sebaceous adenomas (one with cystic component), and history of colon cancer. Gene testing confirmed the diagnosis.

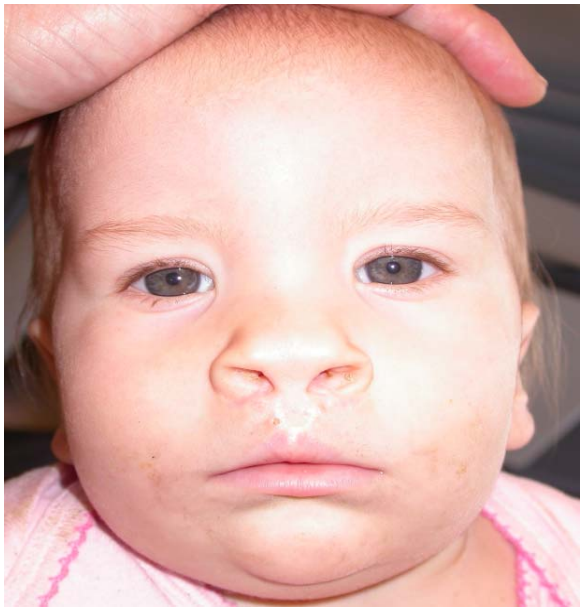




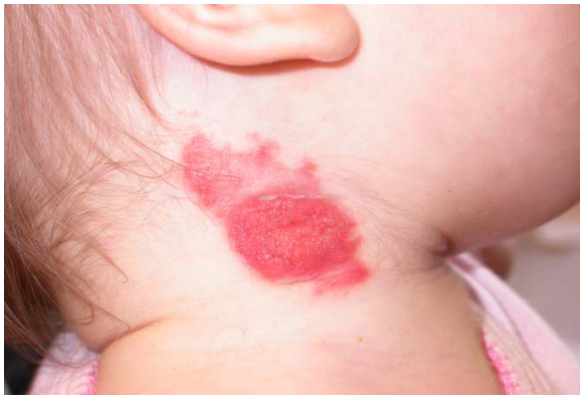


Case 33: Branchio-Oculo-Facial (BOF) Syndrome

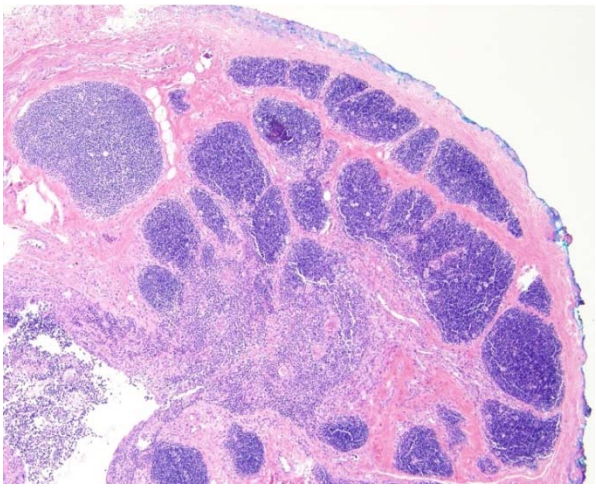
- Clinical Presentation: Characterized by a triad of *b*ranchial, *o*cular, and *f*acial anomalies. Branchial defects are typically cervical along sternoclidomastoids bilaterally, ranging from barely perceptible atrophy to a hairy patch to erythematous hemangiomatous plaques overlying branchial cleft sinuses. Frequent mucus discharge at the sinus ostium is seen with recurrent infections. Dolichocephaly, hypertelorism or telecanthus, broad nasal tip, upslanted palpebral fissures, and cleft lip (or "pseudocleft lip" with prominent philtral pillars), with variable cleft palate (never in isolation) are characteristic.



- Pathophysiology: AD inheritance with near complete penetrance of the TFAP2A gene, encoding transcription factor AP2-α. *de-novo* mutations in 50-60% of cases.



- Pathology: Branchial cleft sinus is a benign dermal sinus with stratified squamous or pseudostratified ciliated columnar epithelium (similar to respiratory epithelium). Ectopic thymus may be seen, as in this case.

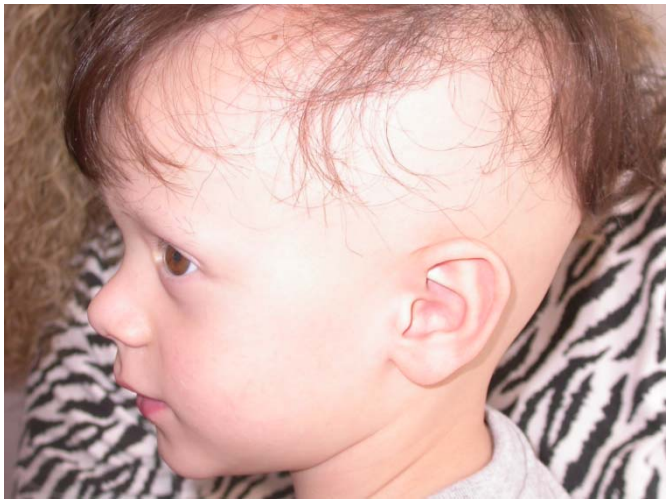


- Diagnosis**:** Based on the presence of some characteristics from all main categories or 2/3 of the main category, plus affected 1st degree relative or presence of ectopic dermal thymus.

- Management: Based on manifestations. Includes ENT for excision of branchial sinuses to prevent recurrent infections. Given the extreme rarity of the syndrome, refer to NCBI GeneReviews Bookshelf for current screening recommendations.

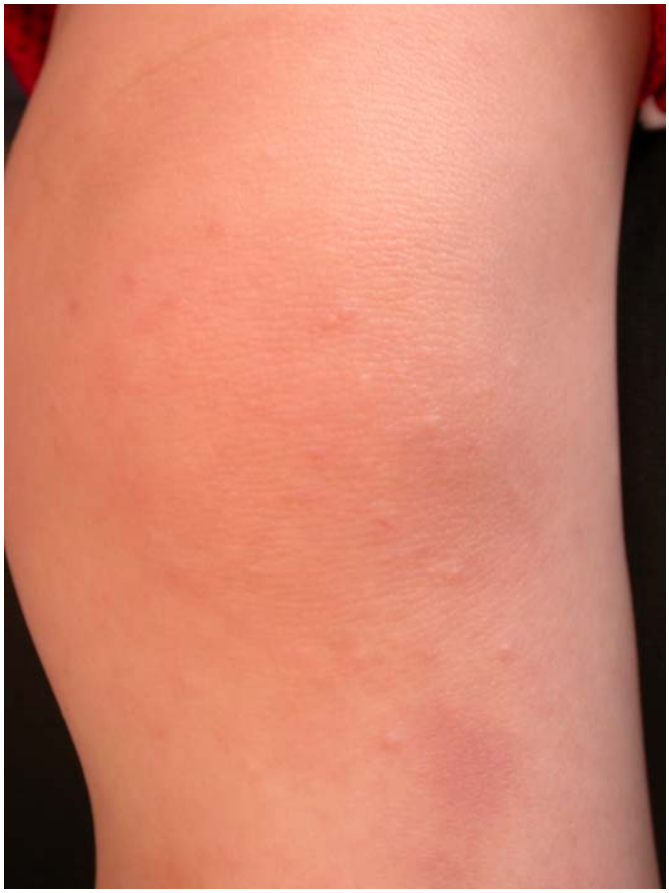
Case 34: Atrichia with Papules

- Clinical Presentation: Permanent loss of hair beginning within the first few months of life with progressive development of widespread skin-colored to milia-like cystic papules predominantly on the scalp, face, and extensor surfaces. These may present simultaneously or later in life.



- Pathophysiology: Autosomal recessive inheritance of mutations involving the zinc finger domain of the human hairless gene on chromosome 8p12. This gene is thought to encode a transcription factor.

- Pathology: In papular lesions, mid-dermal cysts with keratin are seen; analysis of cyst epithelium reveals keratin-15 and keratin-17 suggesting derivation from the follicular bulge and the presence of stem cells. In regions of mature hair loss, cornified follicular cysts replace the isthmus and bulb region.



- Evaluation: Genetic testing can confirm diagnosis. Vitamin D-dependent rickets (secondary to vitamin D receptor gene mutation) must be ruled out, as it can have the same clinico-pathologic phenotype.

- The disorder may be initially misdiagnosed as alopecia universalis; correct diagnosis avoids unnecessary and ineffective treatments.

- The vitamin D receptor gene also encodes a protein with a similar zinc finger domain, thus suggesting a mechanism for the overlapping clinico-pathologic phenotype.

Case 35: LEOPARD Syndrome

- Clinical Presentation: Cardinal features of *L*entigines, *E*KG conduction abnormalities, *O*cular hypertelorism, *P*ulmonic stenosis, *A*bnormal genitalia, growth *R*etardation, and sensorineural *D*eafness.

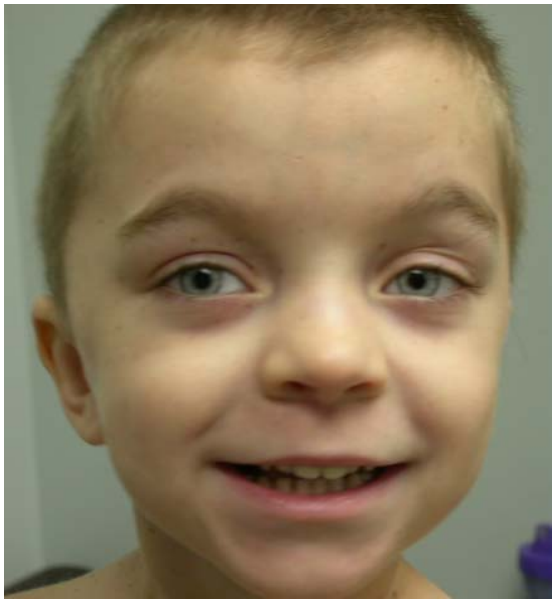
- Pathophysiology: Genetically heterogeneous disorder secondary to mutations in the PTPN11 (90%), *RAF1* (5%), or BRAF (5%) gene. Cases with AD inheritance have high penetrance but variable expression. PTPN11 encodes protein tyrosine phosphatase non-receptor type 11 (SHP-2), a widely expressed signal transduction protein involved in diverse developmental processes. Allelic disorders include Noonan syndrome (*PTPN11*, *RAF1*, or *BRAF*) and cardiofaciocutaneous syndrome (*BRAF*).

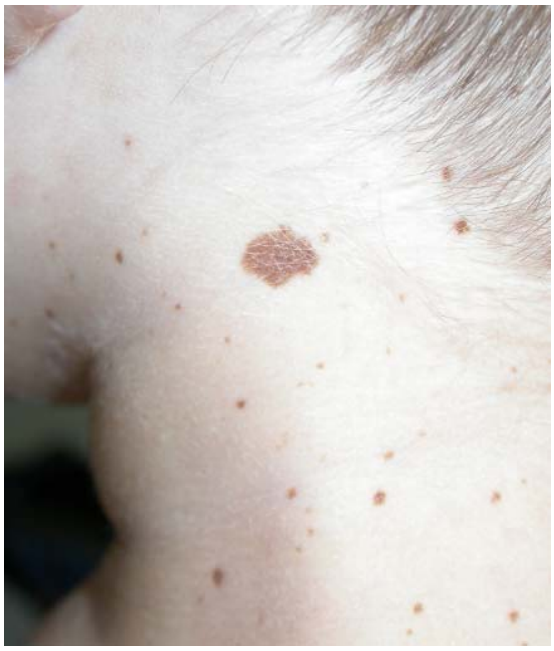
- Diagnosis**:** Confirmed by genetic testing. Must be differentiated from phenotypically similar disorders including Noonan syndrome, cardiofaciocutaneous syndrome**,** and Carney complex.

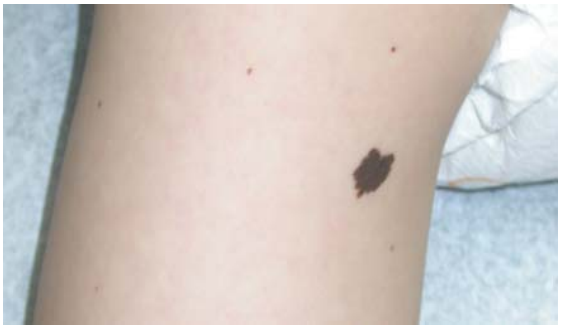
- Management: Early cardiac evaluation is crucial. Phenotypic based management with referral to subspecialists as appropriate.

- Patients with eruptive lentiginosis should always trigger suspicion for a genetic disorder.

- Café noir spots (darker than café au lait macules) are present at birth and usually clinically evident by age 1 year with growth proportional to age (present in 70-80%).







Case 36: Junctional Epidermolysis Bullosa, Non-Herlitz Type

- Clinical Presentation: Mechanically fragile skin with blisters arising from minor trauma. Scaring, milia, dystrophic/absent nails, and scarring alopecia are frequent findings.

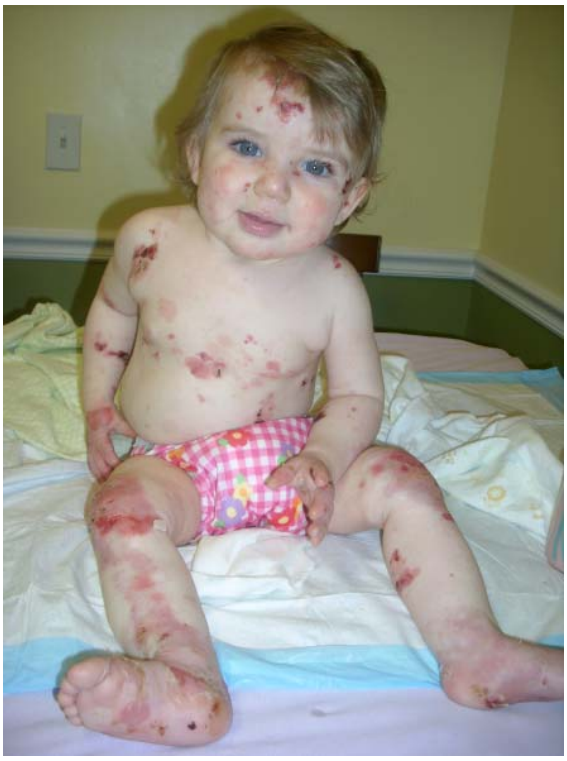
- Pathophysiology: Autosomal recessive inheritance of mutations in genes encoding laminin 332 (formerly laminin 5; Herlitz and non-Herlitz (nH) types), BP180 (nH type, as in this patient), or integrin α6β4 (with pyloric atresia). These comprise anchoring filaments in the lamina lucida.

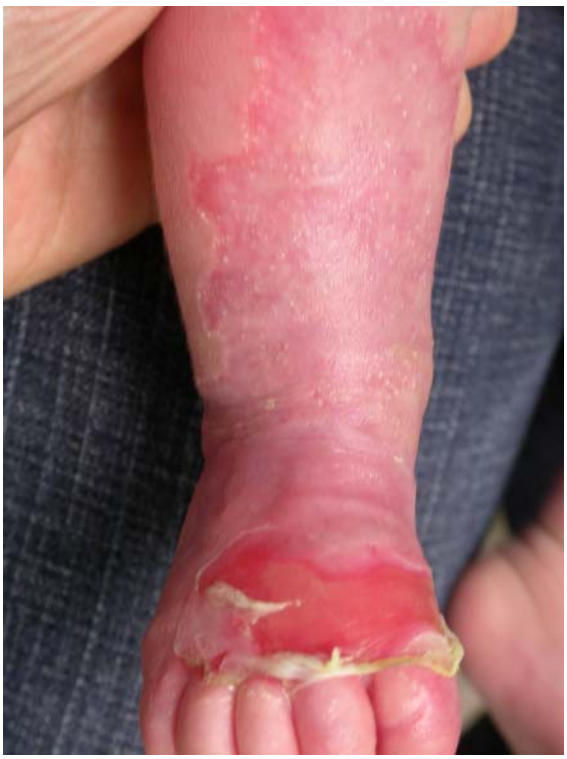
- Pathology: Biopsy of a blister edge for transmission electron microscopy or immunofluorescence antigen mapping to classify subtype. Gene testing is available.

- Prognosis/Management: Patients with non-Herlitz variant can have a normal life span with improvement with age. Herlitz variant is often fatal by age 3-4 years old. Day-to-day therapy involves padding over bony prominences and loose-fitting clothes, daily bleach baths, non-adhesive or "low-tack" dressings (i.e. petrolatum impregnated gauze or soft silicone dressing) for non-infected open blisters/erosions, and silver-impregnated dressings and judicious use of topical and oral antibiotics for infected wounds. Multidisciplinary management for extracutaneous complications if present.

- JEB patients develop dental enamel hypoplasia with risk for extensive caries.

- JEB-nH children are prone to develop large, atypical "EB nevi" with benign histology and biology.





Case 37: Albright's Hereditary Osteodystrophy

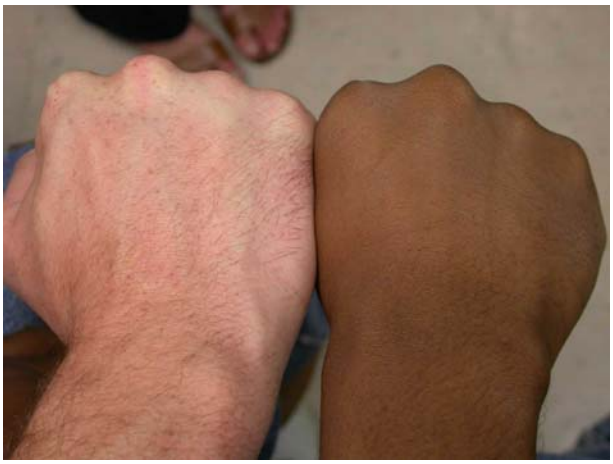
- Clinical Presentation: Distinguished from other causes of cutaneous ossification (osteoma cutis) by its associated clinical findings, including parathyroid abnormalities plus brachydactyly (short metacarpals and metatarsals), short stature, obesity, and round facies.

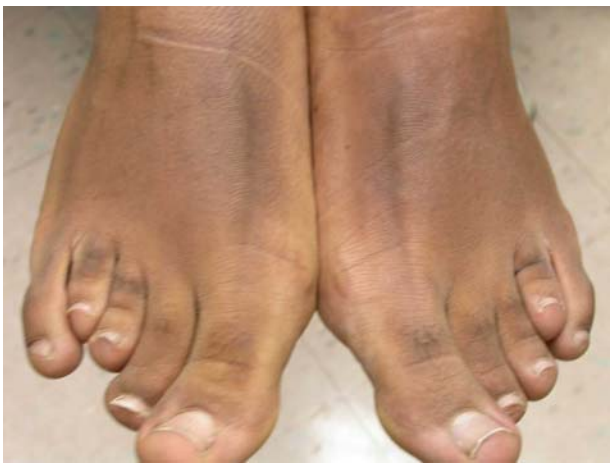
- Pathophysiology: Disease is secondary to epigenetic defects in GNAS1, the gene that encodes the alpha-subunit of the G protein. This protein regulates adenyl cyclase activity, a negative regulator of bone formation.

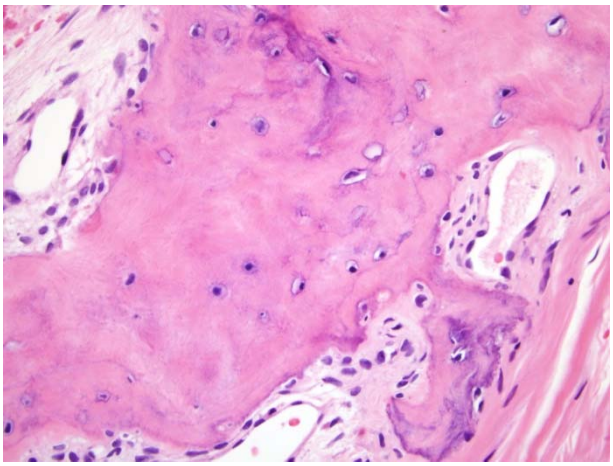
- Pathology: Dermal or subcutaneous bone. As in normal bone, Haversian canals, osteocytes in lacunae, and osteoclasts may be seen.

- Additional workup: Serum calcium, phosphate, parathyroid hormone (PTH), and vitamin D_3 should be measured. Thyroid function tests should be monitored as hypothyroidism may develop. Hypogonadism with corresponding abnormalities in hormones may also be seen.

- Management: Address abnormalities in calcium and/or phosphorus. Surgical removal of painful or symptomatic neoformed bone may be necessary, although recurrence of bony deposits is common.







Case 38: Harlequin Ichthyosis

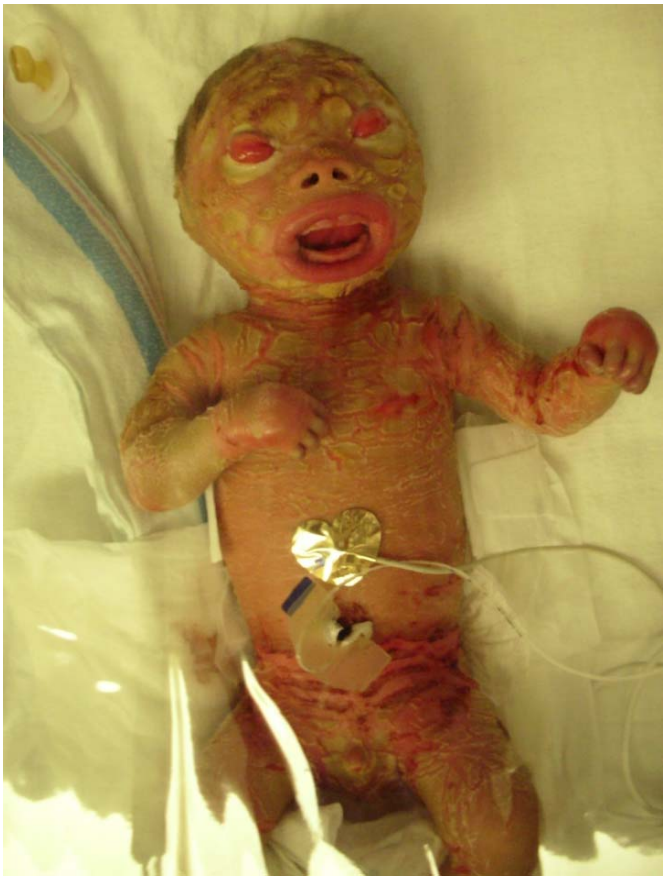
- Clinical Presentation: Massive hyperkeratotic plates with deep fissures in the newborn. Severe ectropion and eclabium are typical. Absent/deformed ears, nose, fingers, and toes often present. Generalized scaling with erythroderma seen in survivors of the neonatal period.

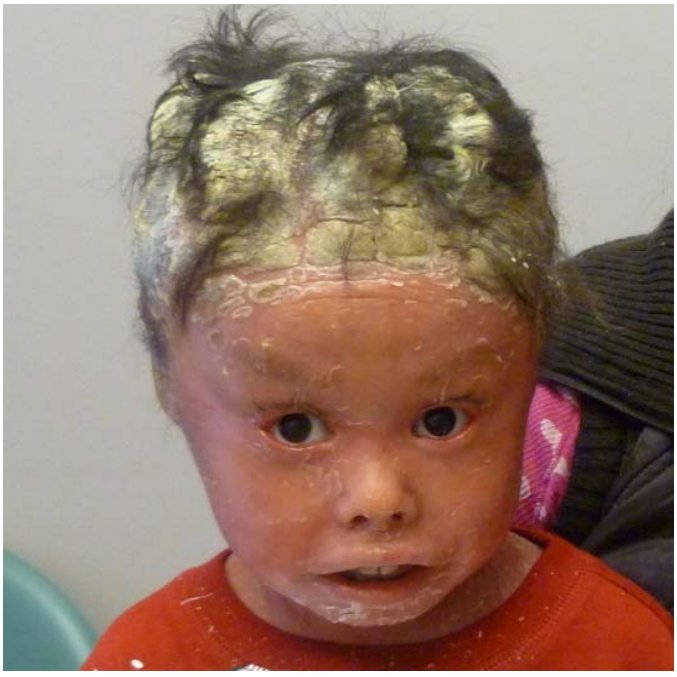
- Pathophysiology: Caused by biallelic loss-of-function mutations in ABCA12, which encodes a transporter that secretes lipids into lamellar granules. Lipid bilayers in the stratum corneum do not form and massive hyperkeratosis results.

- Pathology: Massive hyperkeratosis with or without parakeratosis, often with loss of the granular layer. On electron microscopy, the stratum corneum contains lipids and vacuolar inclusions.

- Management: Intensive care management of body temperature, fluid and electrolyte imbalances, respiratory dysfunction; sepsis is common. Early administration of systemic retinoids, in addition to emollients, assists with shedding and may improve survival. Ophthalmologic referral for management of ectropion.

- Infants are often stillborn or die within the first few days of life secondary to sepsis or respiratory complications. However, survival has improved with advances in intensive care and the use of oral retinoids.





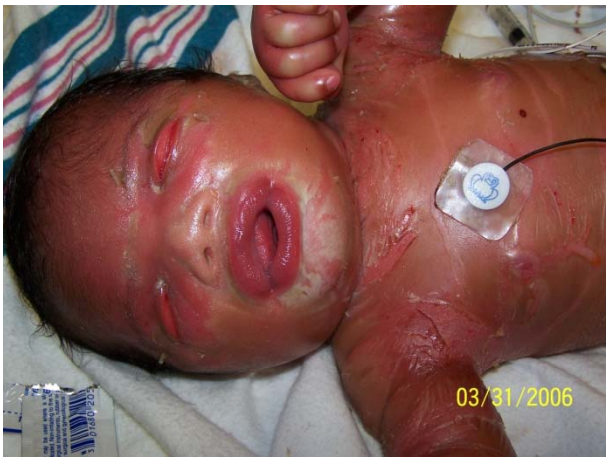
Case 39: Non-Bullous Congenital Ichthyosiform Erythroderma

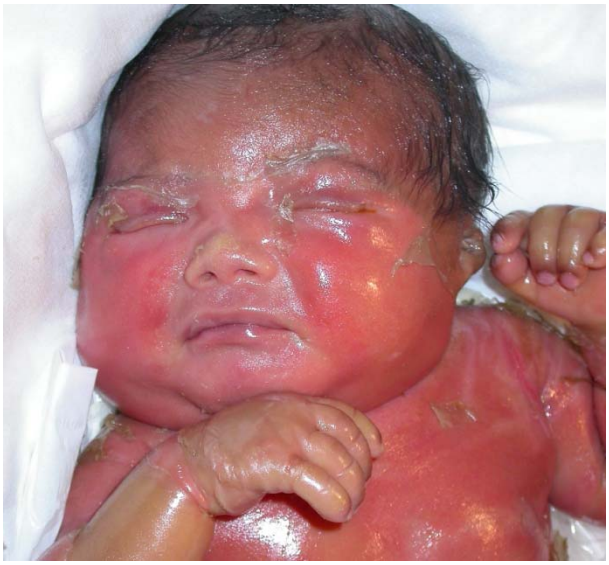
- Clinical Presentation: “Collodion” baby encased in taut, shiny, transparent membrane formed by the aberrant stratum corneum. A few days after birth, erythroderma with fine white scale appears. Diffuse, fissuring keratoderma often develops on palms and soles. Other findings include ectropion and scarring alopecia.

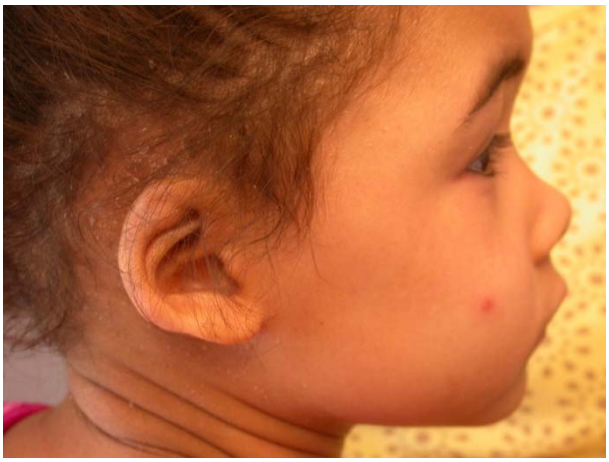
- Pathophysiology: Phenotype is the result of improper development of the cornified cell envelope. Multiple genes, including TGM1, ALOXE3, ALOX12B, and NIPAL4, have been implicated.

- Pathology: Hyperkeratosis, focal parakeratosis and a normal or thickened granular layer. Acanthosis, keratotic follicular plugging, and a mild superficial perivascular infiltrate of lymphocytes in the dermis may be seen.

- Management: Patients need increased intake of fluids, calories, iron, and protein. Oral retinoids reduce scaling but are less effective in suppressing erythroderma. Topical keratolytics, vitamin D_3 derivatives, tazarotene, and formulations containing lactic acid and propylene glycol have also been used.







Case 40: Epidermolysis Bullosa Simplex, Dowling-Meara Subtype with EB Nevi

- Clinical Presentation of Epidermolysis Bullosa, Dowling-Meara type (EB-DM): Grouped hemorrhagic "herpetiform" blisters, often in an arcuate or polycyclic pattern, develop during infancy. Gradual development of diffuse palmoplantar keratoderma is common. Mucosal and nail involvement may also occur. Symptoms can improve with age.

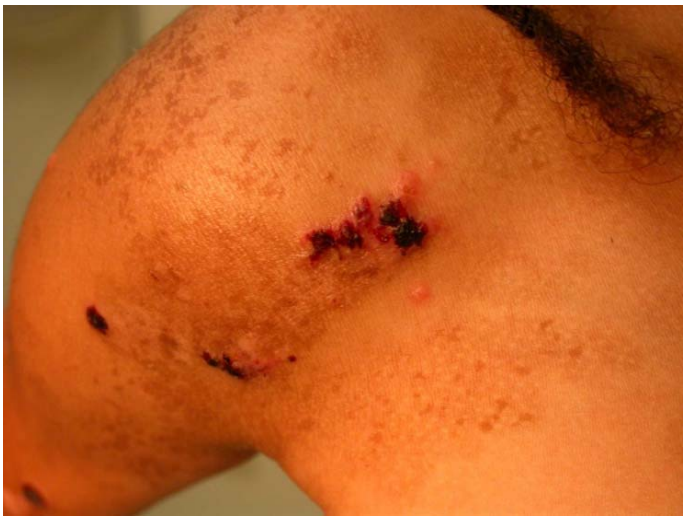
- Clinical Presentation of EB nevi: Children with hereditary EB can develop large, irregularly shaped, darkly pigmented melanocytic nevi that resemble melanoma but are biologically benign. Lesions typically occur at the sites of repeated blisters. Our patient had an EB nevus excised from the right axilla at five years of age.

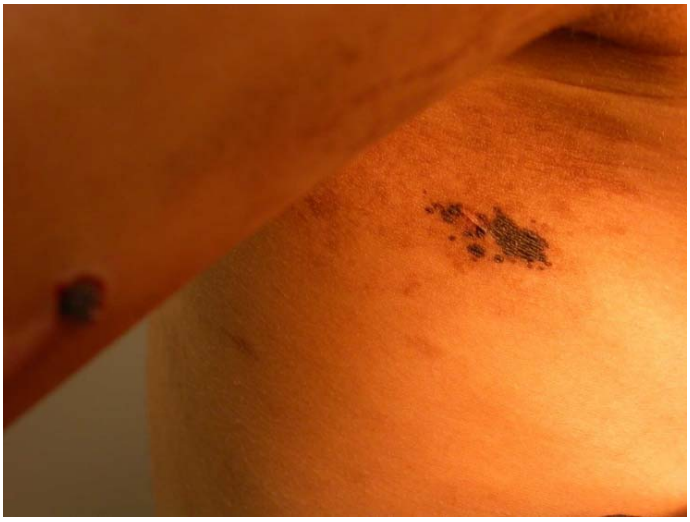
- Pathophysiology of EB-DM: Mutations in the helix initiation and termination motifs of keratin 5 and keratin 14 (codon 125 of K14 frequently involved).

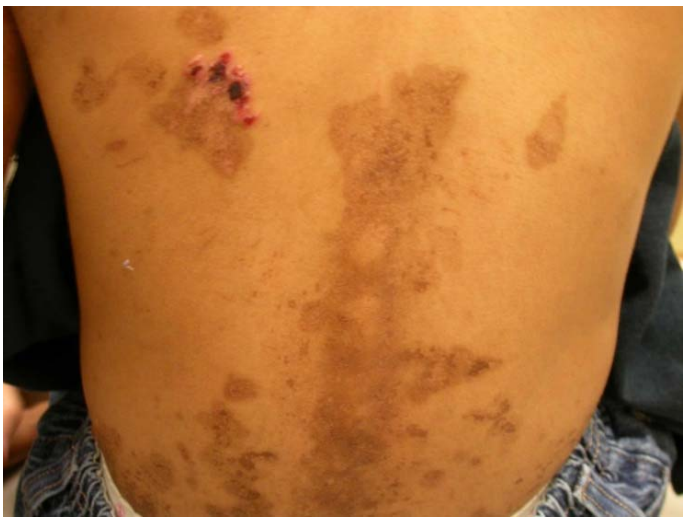
- Pathology of EB-DM: Cleavage in the base of the epidermis, just above the hemidesmosome. Fragments of basal keratinocytes may be present in the blister base. Eosinophils may be found in underlying papillary dermis.

- Pathology of EB nevi: Histologic appearance may resemble compound congenital nevus or persisting nevus/pseudomelanoma pattern.

- Management: Prevention of mechanical trauma and infection.







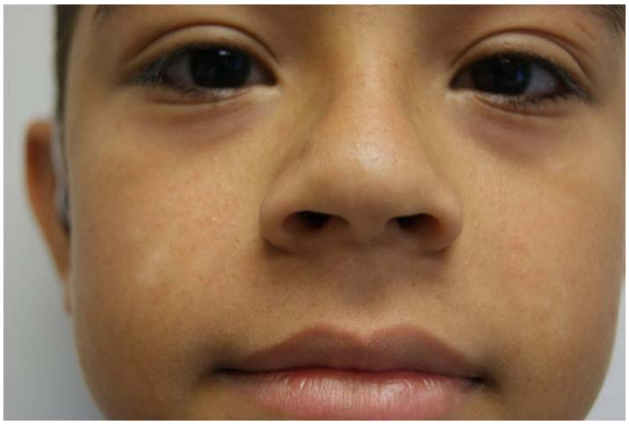
Case 41: Tuberous Sclerosis Complex

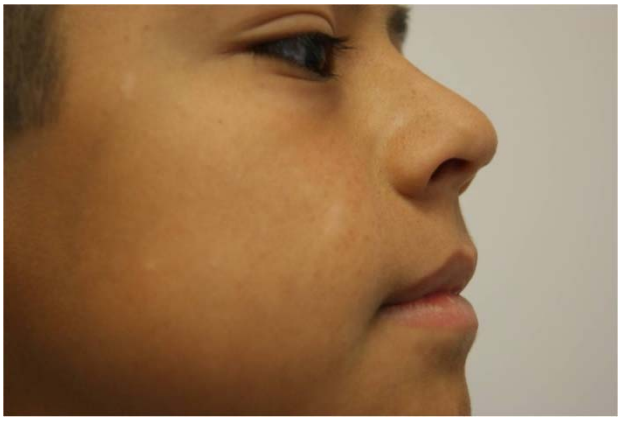
- Clinical Presentation: Children present with a broad range of symptoms due to variable expression, but epilepsy is the most common presenting symptom. Ash-leaf spots are the most common early finding. Forehead plaques and facial angiofibromas are usually present in patients older than 2 years with growth during puberty. Shagreen patches and periungual fibromas are connective tissue hamartomas typically located on the digits and lower back region, respectively.

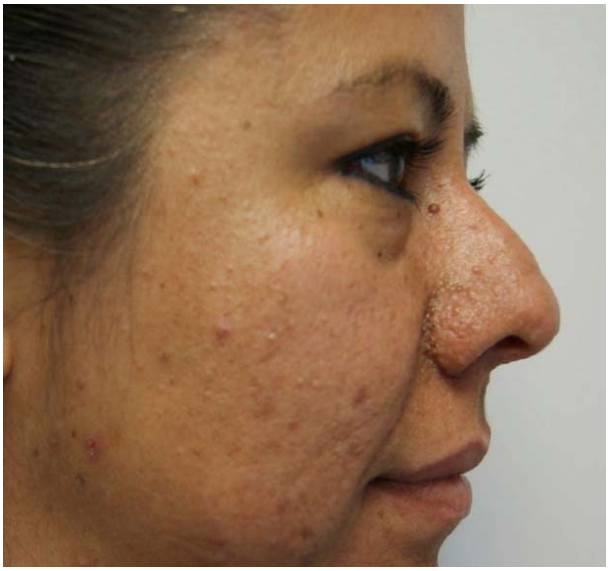
- Pathophysiology: AD inheritance (as in this case), however, 65-75% of cases are due to spontaneous mutations in TSC1 (encodes hamartin) or TSC2 (encodes tuberin). 80-90% of affected patients have a mutation in TSC2, which produces more severe clinical manifestations.

- Pathology: Angiofibromas and periungual fibromas show atrophic sebaceous glands with dermal fibrosis, dilated capillaries, and absent elastin. Shagreen patches show dense, sclerotic collagen bundles with reduced elastic tissue. Ash-leaf macules show normal melanocyte numbers with decreased pigmentation.

- Workup/Associated Conditions:
  - CNS: Cortical tubers and sub-ependymal nodules. The latter may transform into sub-ependymal giant cell astrocytoma
  - Eye: Retinal nodular hamartomas
  - CVS: One or multiple cardiac rhabdomyomas.
  - Lung: Lymphangioleiomyomatosis (40% of females; hormone-sensitive) causing progressive pulmonary cystic cavitations
  - Renal: Angiomyolipomas and renal cysts
  - Psychiatric/developmental: Cognitive impairment, behavioral problems, and a high prevalence of pervasive developmental disorder







Case 42: Basal Cell Nevus Syndrome (BCNS)

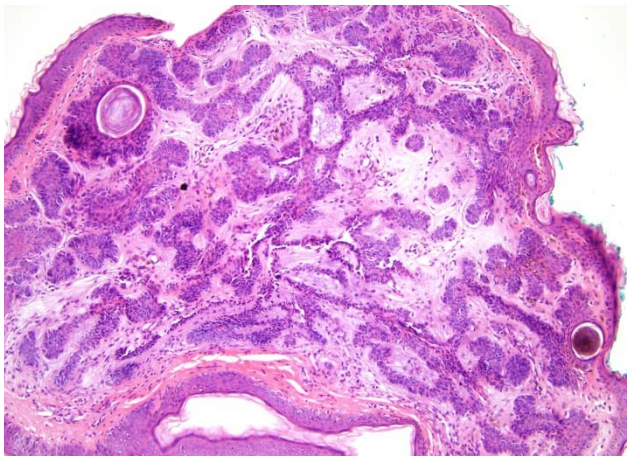
- Clinical Presentation: Numerous BCCs (often at an early age), palmar/plantar pits, odontogenic keratocysts of the jaw (arrow, middle image), characteristic facies (frontal bossing and hypertelorism), calcification of falx cerebri (bottom image), and bifed, fused, or splayed ribs.

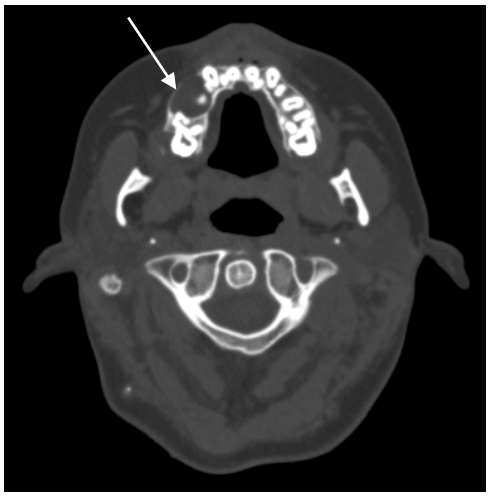
- Pathophysiology: Autosomal dominant inheritance of a mutation of the PTCH gene, an inhibitor of the hedgehog signaling pathway, whose downstream proteins lead to cell growth. UV light exposure appears to be an important cofactor, as BCCs are much more common in sun-exposed areas and less pigmented individuals with the syndrome. Patients are also sensitive to ionizing radiation.

- Pathology: Histologic examination of BCCs cannot distinguish between those with and without the syndrome. Odontogenic keratocysts have the characteristic pathologic feature of a lining with keratinizing epithelium.

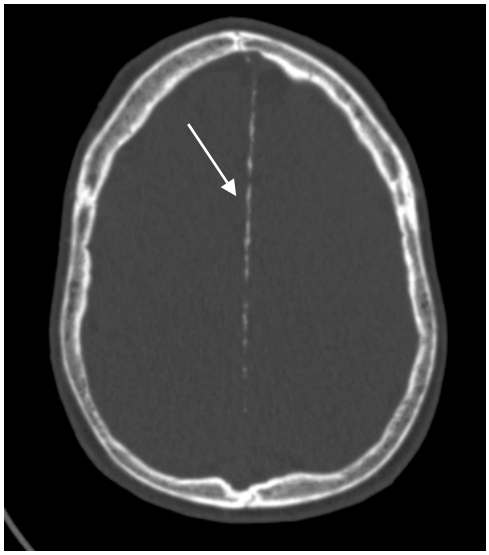
- Workup/Associated Conditions: Because there is an increased risk of ovarian fibromas, pelvic ultrasonography around puberty as a baseline, and then later in life if symptoms develop is recommended. In addition, an annual brain MRI up to age 7 years is recommended to coincide with the peak age of risk of medulloblastoma.

- Cardiac fibromas (3%) and lytic bone lesions of the hands and feet (30% and 17%, respectively) may be seen.





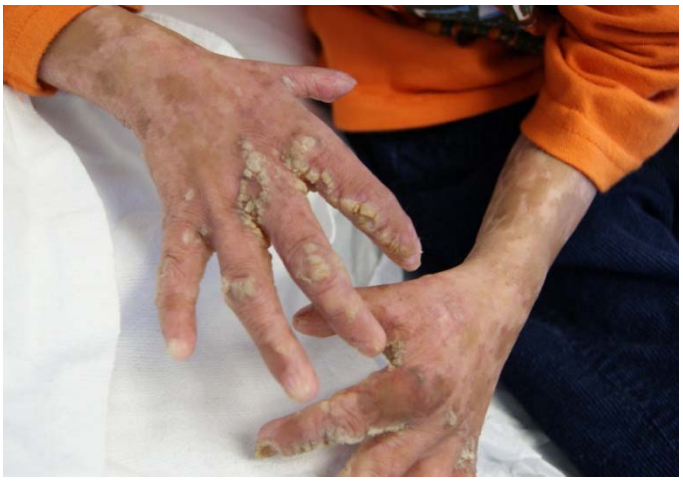
Odontogenic keratocyst



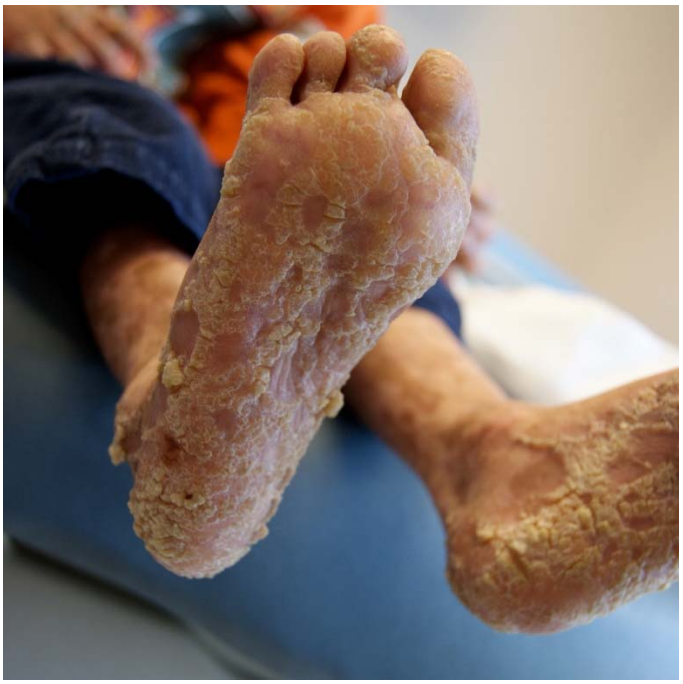
Calcification of the falx cerbri

Case 43: Rothmund-Thomson Syndrome

- Clinical Presentation: Presents in early infancy as a photosensitive eruption composed of erythematous patches and vesicles initially affecting the face and spreading to the buttocks and extremities. It eventually evolves into poikilodermatous skin changes by 3-5 years of age. Other characteristic features include short stature, characteristic facies (frontal bossing, saddle nose, and micrognathia), skeletal abnormalities (may include small hands and feet, absent or malformed radii, and absent or partially formed thumbs), acral keratoses, alopecia, and nail and dental abnormalities.



- Pathophysiology: Autosomal recessive inheritance of a mutation in the *RECQL4* gene. *RECQL4* is a DNA helicase involved in DNA replication and repair.



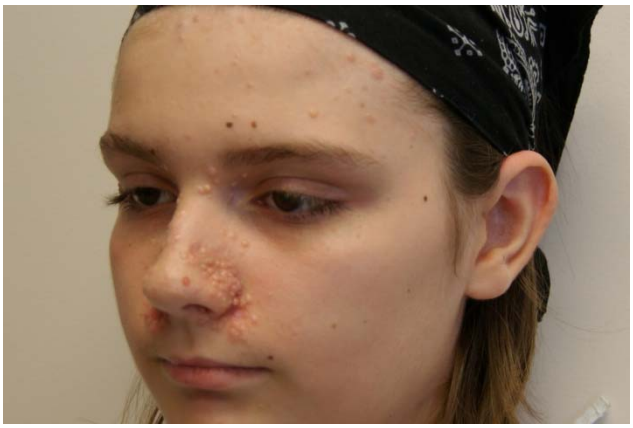
- Pathology: Histologic examination of poikilodermatous skin in children reveals a flattened, atrophic epidermis with papillary dermal edema and dermal vasodilatation, possibly with a perivascular lymphocytic infiltrate. Fragmentation of elastic tissue and loss of appendages appear later.

- Evaluation/Associated Conditions: There is an increased risk of nonmelanoma skin cancer and osteosarcoma (~32%). Baseline skeletal x-rays of long bones by 5 years of age are recommended due to the high frequency of skeletal dysplasias. Young patients should have an annual eye exam to screen for cataracts, as they may occur in 10-50% of patients and most develop between 3-7 years of age. Sexual abnormalities (~25%) may occur and include hypoplasia and/or aplasia of the external genitalia, amenorrhea, lack of secondary sex characteristics, and infertility.

Case 44: Brooke-Spiegler Syndrome

- Clinical Presentation: Presents in late childhood or early adolescence with multiple skin appendage tumors, such as cylindromas, trichoepitheliomas, and spiradenomas, typically located on the head and neck. These grow larger and become more numerous over time. Females are usually more severely affected than males.

- Pathophysiology: BSS shows autosomal dominant inheritance and results from a mutation of the *CYLD* gene. *CYLD* inhibits nuclear factor-kappa B (NF-κB), a transcription factor which protects cells from apoptosis in response to certain signals.



- Pathology: The histolopathologic spectrum is broad and encompasses benign adnexal neoplasms of apocrine, follicular, and sebaceous differentiation, which can occur independently and conjointly. Trichoepitheliomas consist of nests of basaloid cells that lack the myxoid stroma and architectural clefting seen in basal cell carcinoma. Cylindromas show irregularly shaped islands of basaloid cells arranged in a "jigsaw puzzle" pattern, separated by a hyaline sheath. Spiradenomas show a circumscribed dermal nodule with epithelial proliferation containing both small basaloid cells and larger cuboidal cells with eosinophilic cytoplasm. A lymphocytic infiltrate is usually present.

- Evaluation/Associated Conditions: Cylindroma and trichoepithelioma may rarely undergo malignant transformation to cylindrocarcinoma and basal cell carcinoma, respectively. There is an increased risk of salivary gland neoplasms, including adenomas and adenocarcinomas of the parotid glands and minor salivary glands.

Case 45: Common Variable Immunodeficiency

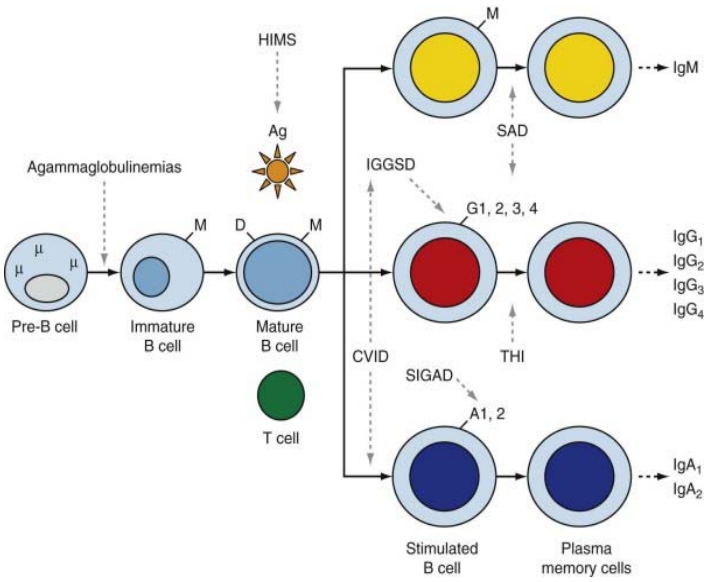
- Clinical Presentation: Recurrent sinopulmonary infections caused by bacterial pathogens is the most common presentation, typically in early adulthood. Lack of response to vaccination is another clue to diagnosis. Autoimmunity, enteropathy and increased risk of lymphomas are additional characteristics of the disease.

- Pathophysiology: CVID is likely a diverse spectrum of immune defects resulting in hypo-gammoglobulinemia (especially IgG) secondary to impaired B-Cell differentiation. Impaired antibody production leads to susceptibility to bacterial pathogens. Although B-Cell numbers are normal, memory cells and plasma cells are decreased.

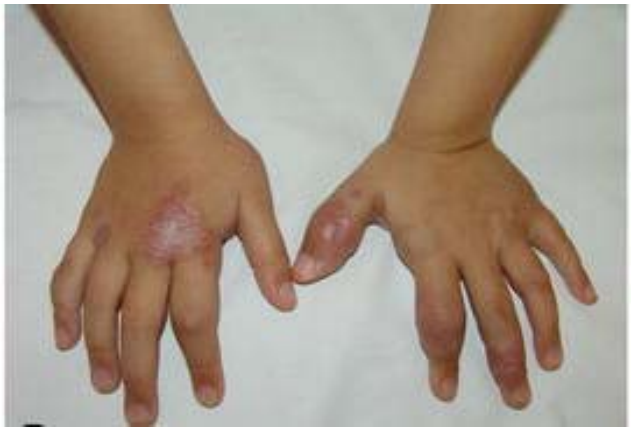
- Evaluation: Quantitative serum Ig levels should be performed. Levels of IgG are often <400 mg/dL. IgA and IgM levels are also generally low. Basic labwork, including CBC, is often normal.

- Management: IVIG, dosed at 300-400mg/kg every 3-4 weeks, is aimed at decreasing infections and other complications, including progression of lung disease.

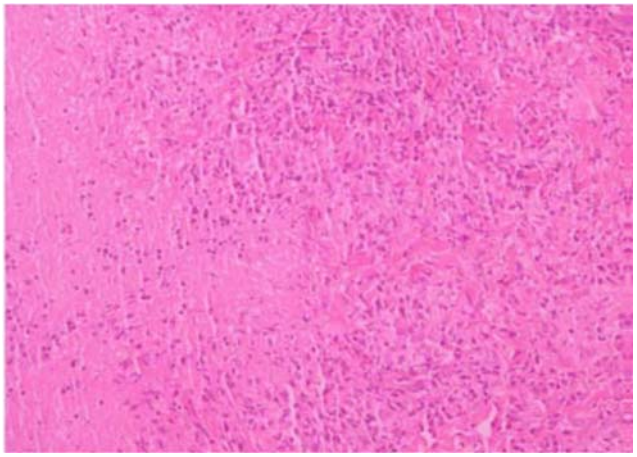
- Lymphoid infiltration of solid organs or skin may occur (see photo), and biopsies demonstrate non-caseating granulomas. Cases of successful treatment of these lesions with TNF-α inhibitors and hydroxychloroquine have been reported.



Long: Principles and Practice of Pediatric Infectious Diseases, 4th ed.



Artac H, et al. Sarcoid-like granulomas in common variable immunodeficiency. Rheumatol Int. 2009 Nov;30(1):109-12.



Artac H, et al. Sarcoid-like granulomas in common variable immunodeficiency. Rheumatol Int. 2009 Nov;30(1):109-12.

Case 46: Klippel-Trenaunay Syndrome

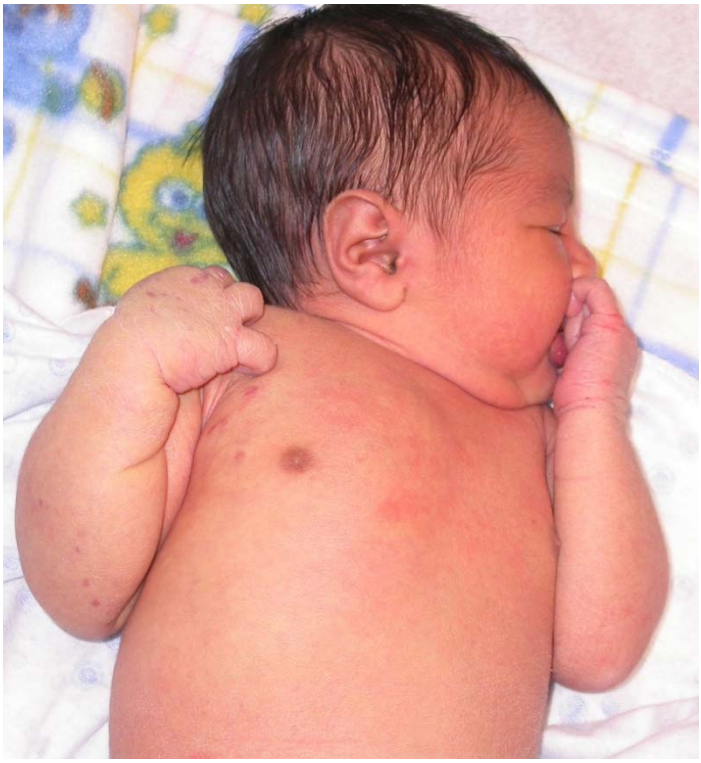
- Clinical Presentation: Capillary and venous malformations with underlying soft tissue and bony overgrowth and limb hypertrophy characterize this condition. Port wine stains are usually visible at birth, and the other features may develop later, or may also be seen on initial presentation. Varicose veins and lymphatic malformations are also common, and may result in significant edema.

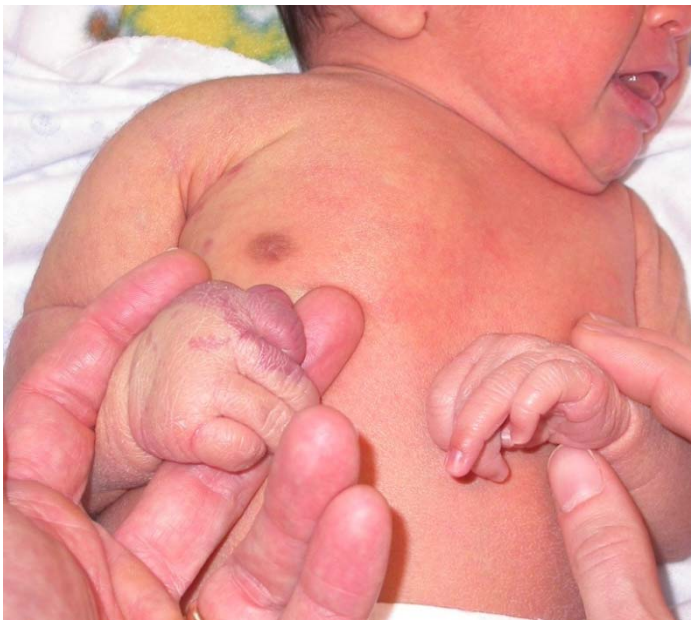
- Pathophysiology: Most cases are sporadic. Dilation and malformation of capillaries, veins, and lymphatics lead to swelling and soft tissue/bony overgrowth, often with hypertrophy of affected limbs.

- Pathology: Nonspecific, demonstrating capillary malformations superficially, which are characterized by dilation and ectasia of small vessels, without increase in number of vessels.

- Evaluation: When clinical findings are suggestive, imaging is the next diagnostic step. MRI and MRV demonstrate the underlying venous and lymphatic malformations and soft tissue changes. Ultrasound can also be considered.

- Management: Compression of affected limbs is important for management of venous stasis and lymphedema. When deep venous malformations are present, DVTs may develop as a complication.





Case 47: Fabry's Disease

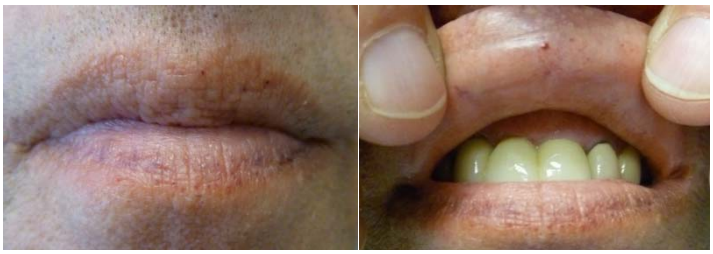
- Clinical Presentation: Classically, affected males develop neuropathy and limb pain in childhood. Cutaneous symptoms follow by the teen years, and include angiokeratomas and telangiectasias in a bathing trunk distribution, as well as thickening of the lips and nose. Hypohidrosis can occur. Renal failure is the most common cause of death, and occurs in middle age.

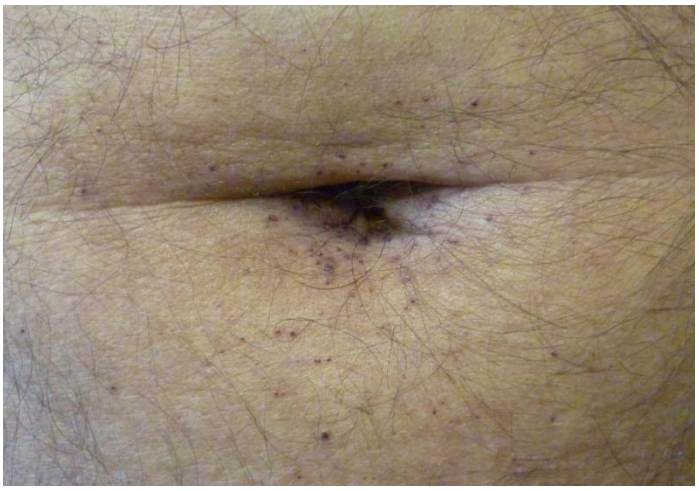
- Pathophysiology: X-linked deficiency of the lysosomal enzyme α-galactosidase A, leading to accumulation of its substrate, globotriaosylceramide in the lysosomes of various tissues. Effects are tissue specific, including endothelium (occlusion/infarction), nervous tissue (neuropathy/cerebral damage), renal tubular cells (renal failure), and cardiac myocytes (cardiomyopathy).

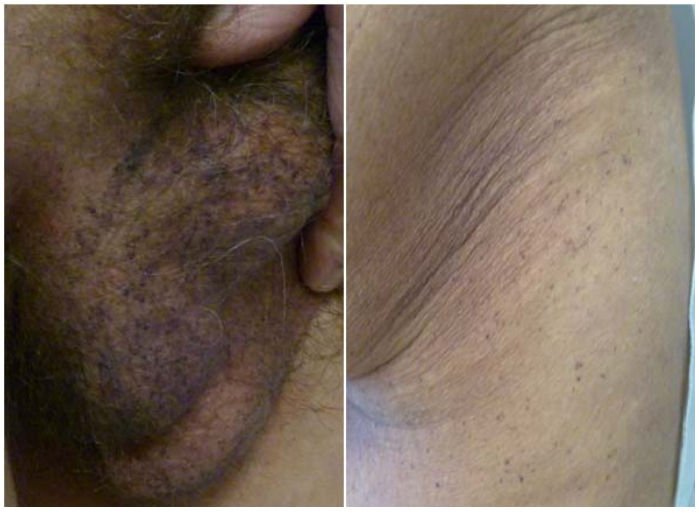
- Pathology: Angiokeratomas demonstrate ectatic, thin-walled vessels, with hyperkeratosis and a thinned epidermis. Diagnostic intracytoplasmic inclusion bodies may be seen with electron microscopy. Deep dermal vessels may show doubly refractile material staining with Sudan black on frozen sections.

- Evaluation: The diagnosis is supported by family history, and can be confirmed by assessment of leukocyte α-galactosidase A activity. Genetic testing is required for diagnosis in females, though mosaic presentations occur.

- Management: Human recombinant alpha-galactosidase, agalsadase beta (Fabrazyme) has been FDA approved for treatment of Fabry's disease, given IV at a dose of 0.2mg/kg every 2 weeks.







Case 48: Focal Dermal Hypoplasia (Goltz Syndrome)

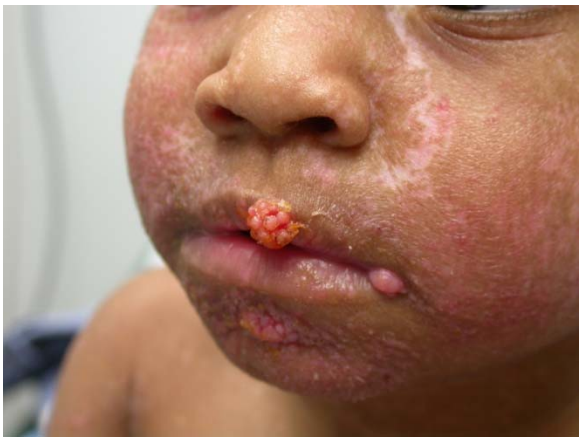
- Clinical Presentation: Reddish-tan, atrophic, often linear or cribiform patches are commonly seen on buttocks, axillae and thighs; these frequently demonstrate fat herniation. Associated abnormalities include ectrodactyly (lobster claw deformity), oral and genital papillomas, colobomas, and abnormal dentition.

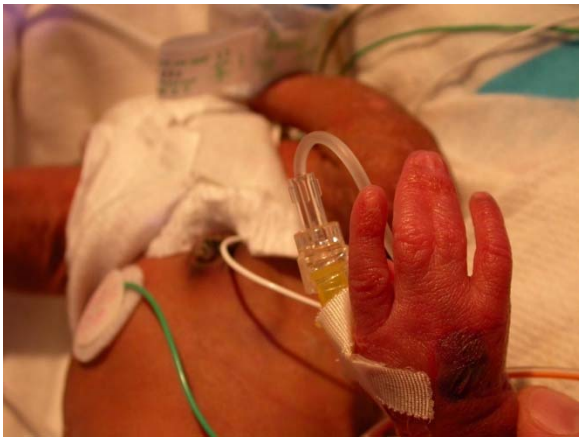
- Pathophysiology: Defects in PORCN, a regulator of Wnt signaling are known to be responsible for this disease; it is inherited in an X-link dominant fashion and is lethal in males.

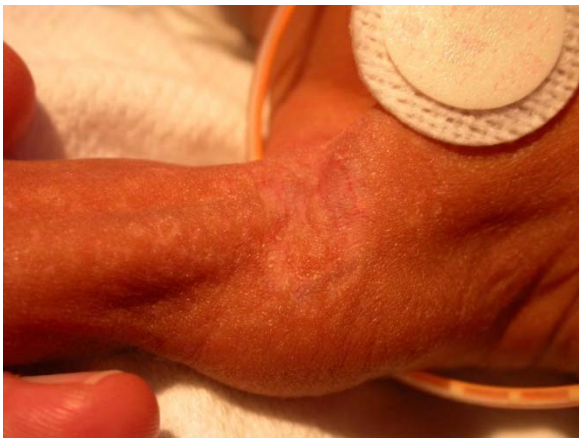
- Pathology: Reduced dermal collagen, telangiectasias and a decreased number of appendages are seen. Fat cells of varying size are often present in the upper dermis.

- Evaluation: Suspicion based on clinical manifestations warrants referral for genetic testing. Radiographic evaluation may reveal osteopathia striata.

- Management: Treatment is supportive with appropriate subspecialist referral based on the associated abnormalities. The telangiectasia may be improved by the pulsed dye laser.







Case 49 & 50: Ehlers-Danlos Syndrome

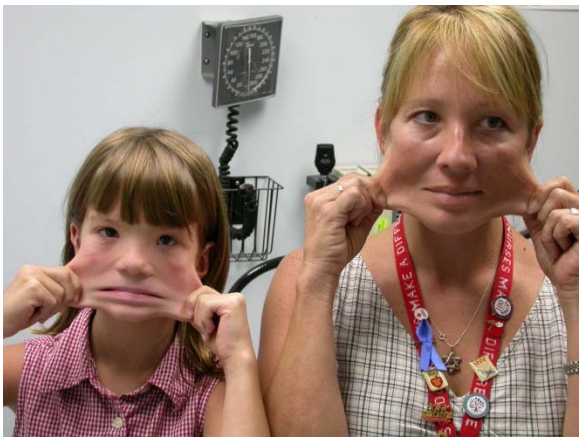
- Clinical Presentation: Typical features include hyperextensible and fragile skin, poor wound healing, molluscoid pseudotumors, easy scarring, and bruising.

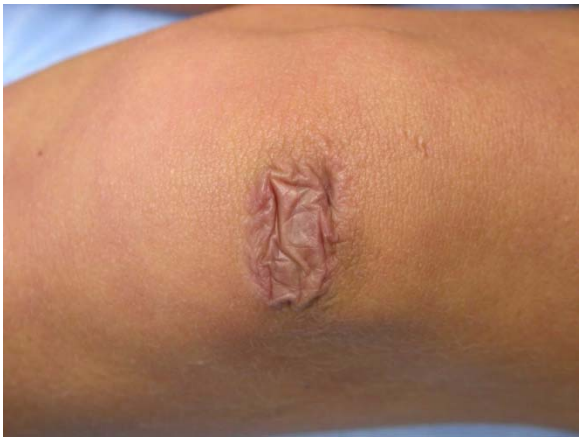
- Pathophysiology: Classically, EDS has been divided into 10 numeric types and the genetic mutations responsible for the various types include defects in collagen (types I, III, and V), tenascin-X, and post translational modification of collagen. Inheritance can be autosomal dominant or autosomal recessive.

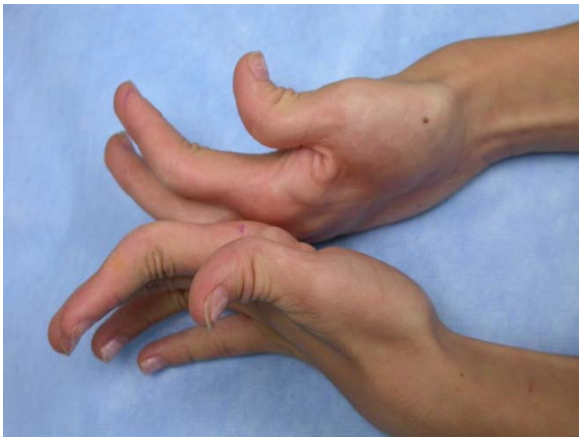
- Pathology: Microscopic examination of the skin may show a thinned reticular dermis and reduced and disorganized collagen fibrils. Non-specific increases in elastic fibrils have been reported, particularly in areas of trauma from molluscoid pseudo tumors.

- Evaluation: Genetic testing and classification of disease into subtypes should be performed, as some involve vasculature and can predispose to life-threatening complications, such as arterial rupture.

- Management: Currently, no specific treatment is available for any of the subtypes of EDS. The most important intervention is monitoring for vascular abnormalities and prevention of trauma to the skin.







Case 51: Werner Syndrome

- Clinical Presentation: Premature aging with appearance of canities, cataracts, osteoporosis, diabetes mellitus, atherosclerosis, and vascular ulcers during the 2nd or 3rd decade. Additional features: sclerodermoid changes, keratoses and ulcerations over bony prominences, short stature, and vascular and soft tissue calcification.

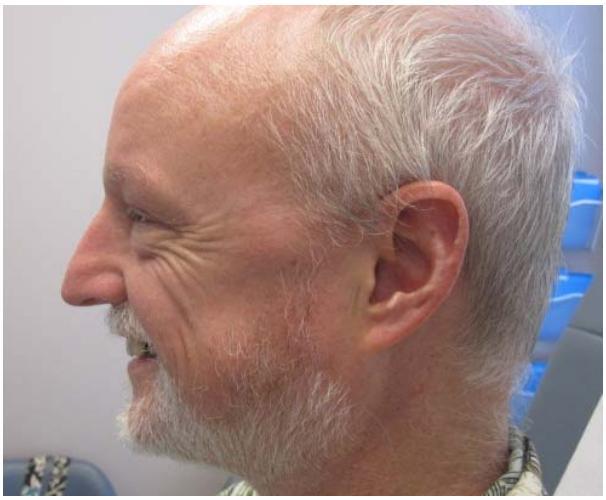
- Pathophysiology: Most cases represent an autosomal recessive inheritance of mutations in the gene RECQL2, which encodes a DNA helicase. LMNA mutations have also been implicated.

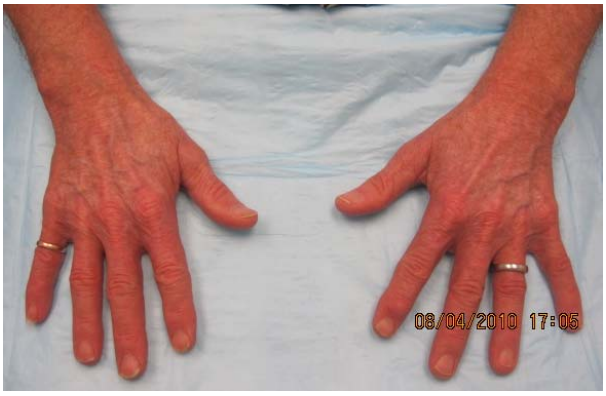
- Pathology: Hyperkeratosis overlies an atrophic epidermis, with focal hypermelanosis of the basal layer. Decreased, atrophic appendages are seen with fibrotic, variably hyalinized dermis. Fat is often atrophic and replaced by hyalinized connective tissue. Vessels may show diabetic angiopathy.

- Evaluation: Genetic testing can confirm diagnosis. Patients should be evaluated for associated conditions (e.g., atherosclerosis, hypertension).

- Management: Individual conditions should be treated with standard therapy.

- Clinical suspicion of this syndrome should arise in the setting of a patient with bird-like facies who appears significantly older than stated age.





Case 52: Congenital Erythropoietic Porphyria

- Clinical Presentation: Severe photosensitivity from birth; marked skin fragility; severe mutilations of face (nose and ears), hands and fingers; facial hypertrichosis; scarring alopecia.

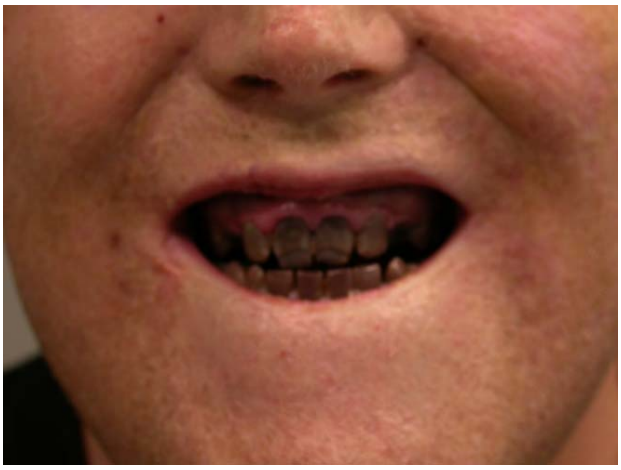
- Pathophysiology: Autosomal recessive deficiency of uroporphrinogen III (UROGEN III) synthase. Multiple mutations have been identified with genotype-phenotype correlations allowing for a spectrum of severity among patients.

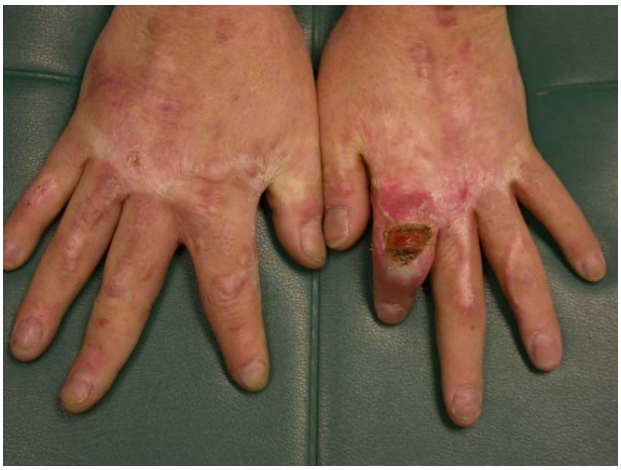
- Pathology: Subepidermal blister without inflammation. Perivascular accumulation of PAS-positive homogenous hyaline porphyrin. Elevated levels of URO-I and COPRO-I in erythrocytes cause hemolysis resulting in porphyrin accumulation in blood, skin, bone, and teeth with excretion in urine and feces.

- Evaluation: In an infant or child with extreme photosensitivity, pink urine in diapers and discolored teeth (erythrodontia) fluoresce under Wood's lamp. Initial screen of plasma porphyrins will be abnormal along with fecal, erythrocyte, and urine assessments.

- Management: Avoidance of sunlight.

- Severe hemolytic anemia and secondary splenomegaly occur. Severely mutilating, but most survive into adulthood.





Acknowledgments

This book and today's presentations are dedicated to two patients that passed away prior to the conference. We greatly appreciate their contribution to our education and future patient care.

Case Presentations to be Given by:
Edith Bowers, MD, PhD
Shelley Cathcart, MD
Meg Daly, MD
Matilda Nicholas, MD, PhD
Kate Roy, MD
Christopher Sayed, MD
Katie Viscusi, MD
Dan Zedek, MD

Special Thanks to:
The UNC Dermatology residents, for their contributions to this book.

Cherie Ezuka, for coordination of the patient presentation day and assistance with this book.

Dr. Lugo-Somolinos and the SEC Committee, for their feedback on and assistance with today's activities.